A.M.A. Journal OF
DISEASES OF CHILDREN

Incidence of Spina Bifida Occulta in Relation to Age
Wataru W. Sutow and Arthur W. Pryde

The Simultaneous Occurrence of Leukemia and Mongolism
William Krivit and Robert A. Good

Meconium Ileus
Harry Shwachman, Charles V. Pryles, and Robert E. Gross

Extramedullary Erythropoiesis in the Livers of Premature Infants
Rodney S. Fowler

Studies in Rheumatic Fever
Joseph A. Johnston

Chlorpromazine in the Treatment of Severe Emotional Disorders of Children
Brian R. Hunt, Thomas Frank, and Thaddeus P. Krush

The Adverse Effects of Early Institutionalization of Mentally Subnormal Children
Malcolm J. Farrell

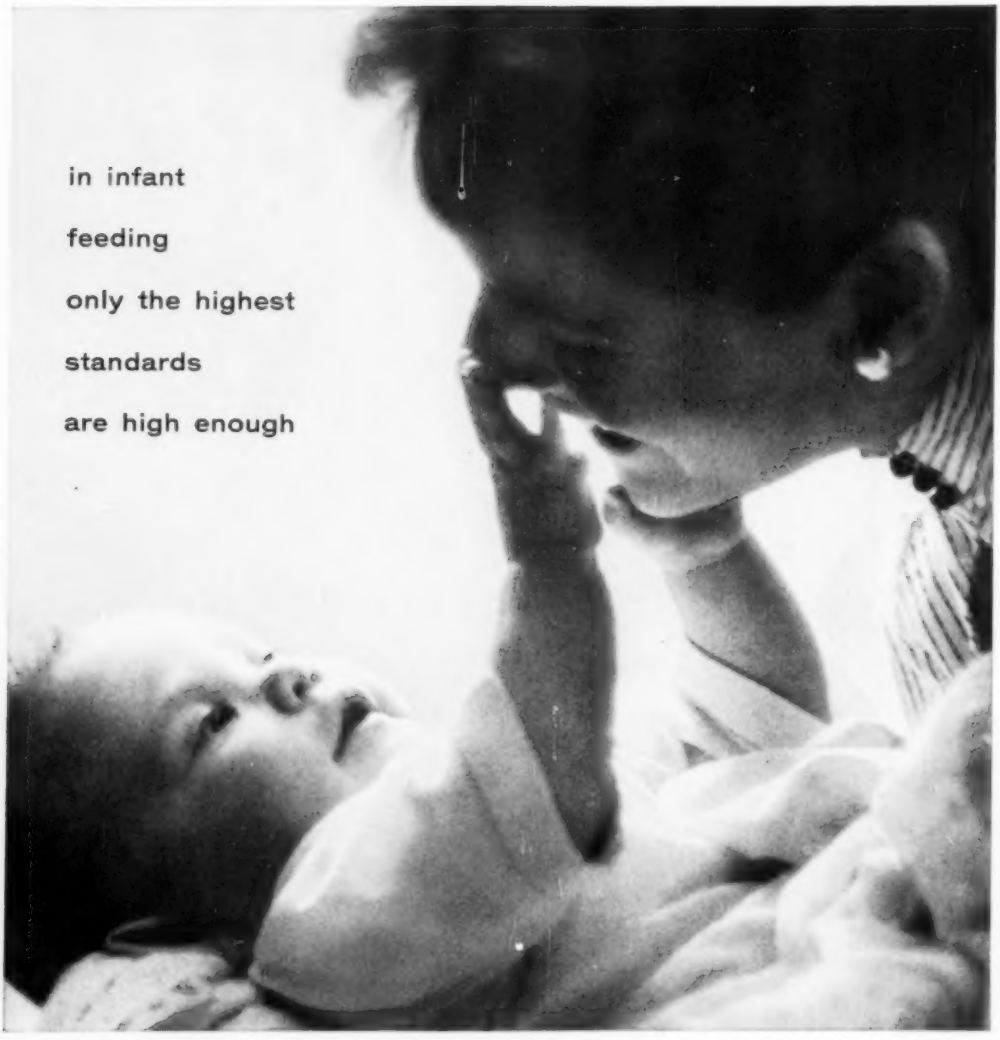
Complete Contents on First Inside Page

MARCH 1956

VOLUME 91 NUMBER 3

From Hayden, p. 287

AMERICAN MEDICAL ASSOCIATION Publication



For 45 years **Dextri-Maltose®**—

Mead carbohydrate manufactured specifically for infant formulas—has been prepared with meticulous care to meet the highest standards of nutritional and pharmaceutical excellence.

MEAD | SYMBOL OF SERVICE IN MEDICINE

MEAD JOHNSON & COMPANY, EVANSVILLE 21, INDIANA, U.S.A.

TABLE OF CONTENTS

VOLUME 91 MARCH 1956 NUMBER 3

ORIGINAL ARTICLES

Incidence of Spina Bifida Occulta in Relation to Age PAGE

Wataru W. Sutow, M.D., Houston, Texas, and Arthur W. Pryde, M.D., Hiroshima, Japan, with the Statistical Assistance of Marvin A. Kastenbaum, M.S. 211

The Simultaneous Occurrence of Leukemia and Mongolism

William Krivit, M.D., and Robert A. Good, M.D., Minneapolis 218

Meconium Ileus

Harry Shwachman, M.D.; Charles V. Pryles, M.D., and Robert E. Gross, M.D., Boston 223

Extramedullary Erythropoiesis in the Livers of Premature Infants

Rodney S. Fowler, M.D., Toronto, Canada 245

Studies in Rheumatic Fever

Joseph A. Johnston, M.D., Detroit 250

Chlorpromazine in the Treatment of Severe Emotional Disorders of Children

Brian R. Hunt, B.M., B.Ch. (Oxon); Thomas Frank, M.D., and Thaddeus P. Krush, M.D., Waltham, Mass. 268

SPECIAL ARTICLES

The Adverse Effects of Early Institutionalization of Mentally Subnormal Children

Malcolm J. Farrell, M.D., Waverley, Mass. 278

CASE REPORTS

Generalized Xanthomatosis with Calcified Adrenals

A. Abramov, M.D.; S. Schorr, M.D., and M. Wolman, M.D., Jerusalem 282

Invagination of the Left Auricular Appendage, Resulting in Sudden Death

William deG. Hayden, M.D.; Carl J. Cramm, M.D.; B. H. Williams, M.D., and James C. Stinson, M.D., Temple, Texas 287

OBITUARIES

Julius Hayes Hess, M.D. 289

REGULAR DEPARTMENTS

Abstracts from Current Literature 290

News and Comment 222, 244, 286, 312

A. M. A.
Journal of Diseases of Children

VOLUME 91 MARCH 1956 NUMBER 3

COPYRIGHT, 1956, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

ROBERT B. LAWSON, Chief Editor
1000 N. W. 17th St., Miami 36, Fla.

ROBERT A. ALDRICH, Portland, Ore.
RICHARD L. DAY, Brooklyn
ROGER L. J. KENNEDY, Rochester, Minn.
FRANCIS SCOTT SMYTH, San Francisco
A. A. WEECH, Cincinnati
WARREN E. WHEELER, Columbus, Ohio
JAMES L. WILSON, Ann Arbor, Mich.
WOLF W. ZUELZER, Detroit

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

AMERICAN MEDICAL ASSOCIATION SCIENTIFIC PUBLICATIONS

A. M. A. Specialty Journals

Monthly

A. M. A. Archives of Internal Medicine. Paul S. Rhoads, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.*

A. M. A. Archives of Dermatology. Herbert Rattner, M.D., Chief Editor, 104 S. Michigan Ave., Chicago. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.†

A. M. A. Archives of Ophthalmology. Francis Heed Adler, M.D., Chief Editor, 313 S. 17th St., Philadelphia 5. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.†

A. M. A. Archives of Surgery. Waltman Walters, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.25.‡

A. M. A. Journal of Diseases of Children. Robert B. Lawson, M.D., Chief Editor, 1000 N. W. 17th St., Miami 36, Fla. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.†

A. M. A. Archives of Pathology. Paul R. Cannon, M.D., Chief Editor, Department of Pathology, University of Chicago, The School of Medicine, 950 E. 59th St., Chicago 37. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.*

A. M. A. Archives of Neurology and Psychiatry. Harold G. Wolff, M.D., Chief Editor, Neurology, 525 E. 68th St., New York 21; Roy R. Grinker Sr., M.D., Chief Editor, Psychiatry, Institute for Psychosomatic and Psychiatric Research, 29th St. and Ellis Ave., Chicago 16. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.50.‡

A. M. A. Archives of Otolaryngology. George M. Coates, M.D., Chief Editor, 1721 Pine St., Philadelphia 3. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.50.‡

A. M. A. Archives of Industrial Health. Prof. Philip Drinker, Chief Editor, Dept. of Industrial Hygiene, Harvard University School of Public Health, 55 Shattuck St., Boston 15. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.*

* Price to students, interns, and residents: $6.00 in U. S. & possessions.

† Price to students, interns, and residents: $7.00 in U. S. & possessions.

‡ Price to students, interns, and residents: $8.00 in U. S. & possessions.

The price for individual copies applies only to this and the previous calendar year; 5 cents additional is charged for each year preceding the last calendar year.

The Journal of the American Medical Association. Weekly. Annual Subscription Price: Domestic, $15.00. Canadian, $17.00. Foreign, $21.50. Price to students, interns, and residents: $9.00 in U. S. & possessions.

Quarterly Cumulative Index Medicus. Issued Twice a Year. Subscription Price, Calendar year, $25.00.

Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 4, 1911, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

"Prompt healing without infection resulted in all traumatic lesions treated"*

". . . Furacin is an effective antibacterial drug which may be safely prescribed for a variety of conditions involving the external eye and lids."

[*BRENNAN, J.W.: AM. J. OPHTH. 35:1343, 1952.]

- rapid, effective antibacterial action against a wide variety of gram-negative and gram-positive organisms with unique lack of irritation
- does not inhibit phagocytosis or retard regeneration of the highly sensitive corneal epithelium
- effective in the presence of pus and mucus
- indicated in external ophthalmic bacterial infections including conjunctivitis, blepharitis, dacryocystitis, keratitis, hordeolum, lid abscesses and for the prevention of post-operative infections

For infections of the nose and ear:

FURACIN nasal—topically effective antibacterial in rhinitis, nasopharyngitis and sinusitis: available in 15 cc. dropper bottles, providing Furacin (brand of nitrofurazone) 0.02% in an isotonic, buffered solution as: FURACIN NASAL WITH EPHEDRINE (with ephedrine • HCl 1%); FURACIN NASAL WITH NEO-SYNEPHRINE† (with phenylephrine • HCl 0.25%).

FURACIN ear solution—prompt antibacterial and deodorizing action in otitis.

FURACIN EAR SOLUTION contains Furacin (brand of nitrofurazone) 0.2% in hygroscopic, water-soluble, polyethylene glycol. Dropper bottle of 15 cc.

†NEO-SYNEPHRINE—REG. TRADEMARK WINTHROP-STEARNS, INC., BRAND OF PHENYLEPHRINE.

FURACIN®

ophthalmic

FURACIN OPHTHALMIC LIQUID (*sterile*) *contains Furacin (brand of nitrofurazone) 0.02% dissolved in an isotonic aqueous solution. Dropper bottle of 15 cc.* FURACIN OPHTHALMIC OINTMENT *contains Furacin (brand of nitrofurazone) 1% in a petrolatum base. 3.5 Gm. tube.*

EATON LABORATORIES, Norwich, N.Y. **NITROFURANS** a new class of antimicrobials neither antibiotics nor sulfas

Instructions to Contributors

Communications regarding editorial management, subscriptions, reprints, etc., should be addressed to Specialty Journals, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript of an article should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. A carbon copy should be retained by the author. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

The main title of an article may not contain more than seventy characters and spaces; a subtitle may be of any length. The subtitle should be sufficiently detached from the main title that a punctuation mark as strong as a colon can be used in the Table of Contents to separate it from the main title; it must not begin with "with."

The author's name should be accompanied by the highest academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

A Case Report must be preceded by an introductory paragraph containing at least thirty words before the details of the case are given. To avert the possibility of legal action, patients' initials and hospital case numbers should not be published.

Material quoted from another publication must be quoted exactly if the original is in English—spelling, capitalization, punctuation, etc., unchanged. Material taken largely from another publication must be credited to the original author, whether quoted exactly or merely abstracted.

Each article should be accompanied by a summary in the present tense, presenting the main points of the article, but in somewhat more generalized terms than in the article itself.

If it is necessary to publish a recognizable photograph of a person, the photograph must be accompanied by written permission of the subject himself if an adult, or of the parents or guardian if a child, to publish his photograph. An illustration which has been published in another publication must be accompanied by written permission from the author and the original publisher to reproduce it in an A. M. A. Specialty Journal.

The maximum illustration allowance is ten illustrations within a total of 100 sq. inches or 8100, whichever is of greater advantage to the author. When no restrictions are placed by the author upon cropping, reducing, and grouping, the publisher is often able to use twenty or more illustrations in one article with the 8100 allowance. See an issue of this journal for examples. Oversized originals should be photographed and a print submitted. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author.

Any cut-off marks should be made on the margins (or mountings) rather than on the illustration itself. Charts and drawings should be in black ink on hard, white paper. Lettering must be large enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, an abbreviated title of the article, and top plainly indicated. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the Quarterly Cumulative Index Medicus, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the Quarterly Cumulative Index Medicus. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation or all be in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

Matter appearing in the A. M. A. Specialty Journals is covered by copyright, but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. Specialty Journals, or in any other publications issued by the Association, will not be permitted.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

"a highly effective antiemetic
. . . for use in children."[1]

THORAZINE* *chlorpromazine, S.K.F.*

The effectiveness of 'Thorazine' for the control of vomiting in children has been confirmed by a number of clinicians. Results in refractory cases have been particularly dramatic.[1-5]

'Thorazine' is available in ampuls, tablets and syrup, as the hydrochloride; and in suppositories, as the base.

'Thorazine' should be administered discriminately; and, before prescribing, the physician should be fully conversant with the available literature.

Pediatric Bibliography

1. Wikler: The Use of Chlorpromazine as an Anti-emetic in Children, Arch. Pediat. 72:197 (June) 1955.
2. Daeschner et al.: Chlorpromazine in the Control of Vomiting in Children, Am. J. Dis. Child. 89:525 (May) 1955.
3. Steigman and Vallbona: Chlorpromazine, A Useful Antiemetic in Pediatric Practice, J. Pediat. 46:296 (March) 1955.
4. Steigman and Vallbona: Experience with Chlorpromazine in Pediatrics, Internat. Rec. Med. & Gen. Pract. Clinics 168:351 (May) 1955.
5. Moyer et al.: Clinical Studies of an Anti-emetic Agent, Chlorpromazine, Am. J. M. Sc. 228:174 (Aug.) 1954.

*T.M. Reg. U.S. Pat. Off.

Smith, Kline & French Laboratories, Philadelphia

little

How to win friends ...

The Aspirin that Tastes So Good.

The Flavor Remains Stable down to the last tablet.

15¢ Bottle of 24 tablets (2½ grs. each).

We will be pleased to send samples on request.

THE BAYER COMPANY DIVISION

of Sterling Drug Inc.

1450 Broadway, New York 18, N. Y.

Oatmeal
in the light of Current Nutritional Knowledge

In pediatric nutrition oatmeal, with its easy digestibility and assimilation, and its wealth of essential nutrients, merits recommendation among the first solid foods as soon as spoon-feeding can be instituted.

Present nutritional knowledge, greatly advanced during the past two decades, again enhances the time-honored position of this widely eaten breakfast dish—rolled oats with milk and sugar.

The protein content of oatmeal, unaffected by processing or preparation for the table, is higher than that of other commonly eaten whole-grain cereals. The protein of the oatmeal and milk serving is of high biologic value. The carbohydrate is readily digested and available for energy needs.

Among whole-grain cereal foods, oatmeal ranks among the highest in thiamine. It also contributes notable amounts of other B-complex vitamins.

For mineral content, too, oatmeal is rated among the leaders. It is outstanding for iron and phosphorus.

The low cost of Quaker Oats and Mother's Oats, their delicious nutlike flavor, assured by careful selection of the oats used, together with their high nutrient value, warrant the physician's continued recommendation of oatmeal as a key dish of America's breakfast.

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by the Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned (cooks in 5 minutes) varieties which are of equal nutrient value.

The Quaker Oats Company
CHICAGO

HARRY C. MOORES

CHAIRMAN OF THE BOARD

announces: on March 1, 1956

THE NAME OF

M&R LABORATORIES

WILL BE CHANGED TO

ROSS LABORATORIES

This action is taken in the tenth year after the death of Stanley M. Ross, to commemorate the contribution of the co-founder of our company. The career of Mr. Ross coincided with the development of pediatrics as a science. Through close liaison with the physician and the research scientist, men of industry such as Mr. Ross aided in the development and application of new knowledge in scientific infant feeding that resulted in a constant reduction in the incidence of nutritional problems and consequent infant mortality.

The change in name signifies no change in organization, in personnel or in policy. On the contrary, we herewith reaffirm the principles which have guided us during the past 53 years.

Promotion of our product, Similac, will be restricted, as it always has been, to the medical professions. We hold inviolate the prerogative of the physician to prescribe infant feeding according to his judgment, and believe that only he has the training and experience necessary to select and prescribe the formula and other elements of the dietary, and to direct the preventive care of the infant.

Because of the close interrelation between nutrition and disease states, and because nutrition becomes particularly critical in disease conditions, the proper application of the findings from research in nutrition requires the special skill of a

physician. The infant's parents in general are not equipped (while the physician is):

(1) to judge the adequacy of research quoted in support of claims for infant feeding products,

(2) to evaluate the conclusions drawn from the data presented,

(3) to determine whether the evidence is cited in context,

(4) to view the findings presented in proper perspective.

Ross Laboratories believe that no action should be taken to produce pressures from lay sources designed to influence the physician's prescription of product or application of medical concept. Efforts to create brand preference or to publicize medical concepts for commercial gain through the use of mass media can only result in undesirable pressure on the physician from patients. Lay advertisement of brands of infant formulas or foods intended for the first year of life infringes on the right of the physician to prescribe as his judgment directs.

We believe it incumbent on Ross Laboratories to encourage and to participate in fundamental and applied research in the field of nutrition. The M & R Pediatric Research Conference program will be carried on as the Ross Pediatric Research Conferences. This program is but one instrument for achieving this objective. We shall continue with renewed vigor our efforts to provide means for further enhancement of the practice of medicine for infants and children.

H. C. Moore.

ROSS LABORATORIES *COLUMBUS 16, OHIO*

Meat...

and Adequate Protein Nutrition in Early Childhood

During the second and third years of childhood the skeletal muscles should increase by about one-third.[1] Diets deficient in protein, however, may permit little or no muscle increment. As a result of such diets the child displays an habitual fatigue posture and low vigor.

Foods which contribute valuably to the protein, B vitamin, and mineral needs of the young child include meat (beef, lamb, pork, veal), liver, poultry, fish, milk, cheese and other dairy products. Recommended weekly diets provide one daily serving of lean muscle meat for six days and one serving of liver for one day.[2,3]

Meat protein, approximating 25 per cent of cooked lean meats of beef, lamb, pork, and veal, is high in biologic value. The table shows the valuable amounts of nutrients supplied by one ounce of the respective meats and of liver. Pork is especially notable as an outstanding source of thiamine. By accustoming the child to a variety of flavors and textures, the many kinds and cuts of meat serve well in the development of good eating habits which carry over into subsequent years.[3]

1. Stearns, G.: Assessment of the Incidence of Nutritional Deficiency in Infants, Children and Adolescents (Proceedings of the National Food and Nutrition Institute), Washington, D.C., Agricultural Handbook No. 56, United States Department of Agriculture, 1953.

2. Nelson, W. B.: Textbook of Pediatrics, ed. 6, Philadelphia, W. B. Saunders Company, 1954, p. 122.

3. Martin, E. A.: Roberts' Nutrition Work with Children, Chicago, The University of Chicago Press, 1954, pp. 225-228.

4. Watt, B. K., and Merrill, A. L.: Composition of Foods—Raw, Processed, Prepared, Washington, D.C., United States Department of Agriculture, Agricultural Handbook No. 8, 1950.

Nutrient and Caloric Contribution of One Ounce of Cooked Meats[4]

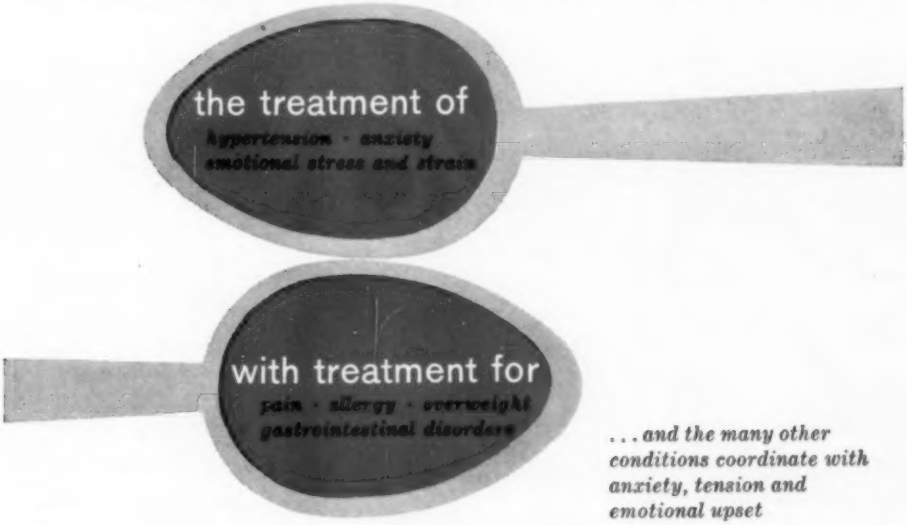
	Protein	Thiamine	Riboflavin	Niacin	Phosphorus	Iron	Calories
Beef round	7.7 Gm.	0.02 mg.	0.06 mg.	1.6 mg.	64 mg.	1.0 mg.	77
Lamb, leg roast	6.7 Gm.	0.04 mg.	0.07 mg.	1.5 mg.	73 mg.	0.9 mg.	66
Pork loin	6.7 Gm.	0.24 mg.	0.07 mg.	1.4 mg.	67 mg.	0.9 mg.	95
Veal, shoulder roast	8.0 Gm.	0.04 mg.	0.09 mg.	2.2 mg.	73 mg.	1.0 mg.	64
Beef liver*	6.7 Gm.	0.08 mg.	1.13 mg.	4.2 mg.	138 mg.	2.2 mg.	59*

*Also, 15,165 I.U. vitamin A.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute
Main Office, Chicago... Members Throughout the United States

when you must combine...



...and the many other conditions coordinate with anxiety, tension and emotional upset

prescribe compatible

pleasant-tasting
highly compatible liquid
compounded with...
other agents
of your choice

The antihypertensive and tranquilizing effects of Serpasil can now be easily combined with other agents that you may wish to prescribe simultaneously. Serpasil Elixir is compatible with many other medications, such as Pyribenzamine® citrate (tripelennamine citrate CIBA) Elixir, dextro-amphetamine sulfate elixir, codeine phosphate, ephedrine sulfate, and sodium salicylate.

Each 4-ml. teaspoonful of light green, lemon-lime flavored Serpasil Elixir contains 0.2 mg. of Serpasil.

C I B A
Summit, N. J.

s/2250M

Report | from Carnation Research Laboratory

Carnation Research Laboratory, 8015 Van Nuys Boulevard, Van Nuys, California

General Research

For a half century, Carnation has conducted a continuous and expanding 5-phase research program in dairy and cereal products. Newest major research facility is the Carnation General Research Laboratory at Van Nuys, California – one of America's most modern laboratories devoted exclusively to product research.

Qualified Scientific Staff

At the Van Nuys Laboratory alone, a large Carnation staff of graduate scientists represents an extremely broad background; fields covered include biology, bacteriology, parasitology, chemistry, biochemistry, organic chemistry, food technology, dairy husbandry, dairy technology, dairy bacteriology, dairy manufacturing and agricultural engineering.

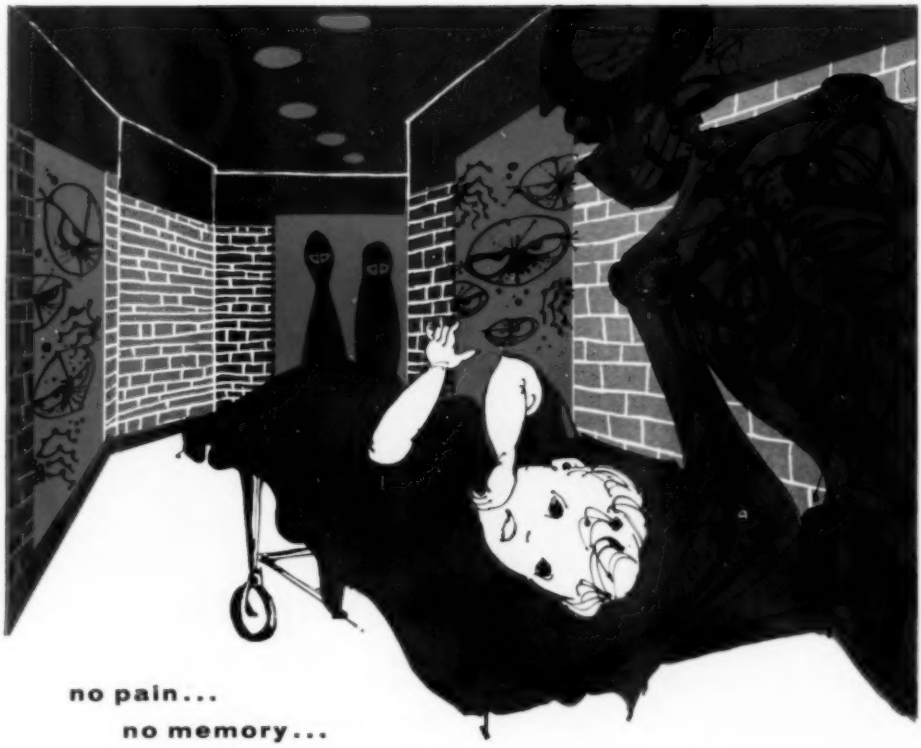
Continuous, Planned Research

protects the uniform high quality of both established and new Carnation products.

CARNATION PROTECTS YOUR RECOMMENDATION WITH CONTINUOUS 5-PHASE RESEARCH:

Carnation Research Laboratory,
Carnation Farms,
Carnation Plant Laboratories,
Carnation Central Product Control Laboratory,
Carnation-sponsored University and Association Research.

"from Contented Cows"



no pain...
no memory...

No Nightmare of Fear

in pediatric anesthesia

With PENTOTHAL® Sodium administered rectally, the child goes to sleep in his own bed . . . awakens there after surgery with complete amnesia of the events between. Not for him the strange and terrifying world of the operating room to linger disturbingly in his memory. In relation to this problem, Whyte[1] has written, "it would be ideal if every child about to undergo any operative procedure could be given rectal PENTOTHAL as a basal narcosis."

And because Rectal PENTOTHAL reduces the dosage of inhalation and supplementary agents, after-effects are markedly lessened. As a basal anesthetic, as a sole agent in minor procedures, PENTOTHAL by rectum offers a notably safe, simple and humane approach to pediatric anesthesia.

Abbott

PENTOTHAL® SODIUM

(Thiopental Sodium, Abbott)

603145

[1]Whyte, D. W., "Special Indications for Rectal Pentothal in Children", *Canad. Med. J.*, 64:525, June, 1951

Enriched Bread...

in Tween-Age Nutrition

Food consumed by the tween-ager, though satisfying hunger, may fall far short of satisfying nutrient needs for optimal growth.[1] The diet "unbalanced" in nutrients is considered as injurious as underfeeding. Such misfeeding, persisted in during the years when the growth impulse is strong, ultimately produces an adult body of inferior physique and vigor.[1]

Enriched Bread, repeatedly endorsed by nutrition authorities for its contribution to improved nutrition and health in America's children,[2] constitutes an important nutritional buttress for the tween-ager's diet.

Its protein—wheat flour protein supplemented with milk and yeast proteins—effectively promotes growth as well as tissue maintenance. Its B vitamins and iron (standardized at levels prescribed by government regulations) help in assuring adequacy of these essentials in the diet. Its carbohydrate by "sparing" protein aids in protein utilization.[3]

Enriched bread—offering much nourishment at little cost—may well provide a higher percentage of the calories needed by the tween-ager.[4]

1. Martin, E. A.: Roberts' Nutrition Work with Children, Chicago, The University of Chicago Press, 1954, p. 141.
2. The Addition of Specific Nutrients to Foods, Public Health Reports *69*:275 (Mar.) 1954.
   Kelly, H. T.: Impact of Modern Nutrition on Twentieth Century Morbidity, Pennsylvania M.J. *58*:481 (May) 1955.
3. Cantarow, A., and Trumper, M.: Clinical Biochemistry, ed. 5, Philadelphia, W. B. Saunders Company, 1955, pp. 139, 140.
4. Sherman, H. C.: Food Products, ed. 4, New York, The Macmillan Company, 1948, pp. 221, 222.

AMERICAN BAKERS ASSOCIATION
20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

Efficient milk replacement

for the milk-allergic infant

Practical equivalent of milk

Gerber Meat Base Formula closely approximates evaporated milk in complete proteins, carbohydrates, fats and minerals. To be fed through regular nursing bottles.

Well tolerated by infants

Clinical studies* indicated "infants accepted meat base formulas well. Fewer patients were sensitive to meat than legumes." Incidence of digestive upsets low.

Normal growth and development assured

Authoritative report* substantiated the nutritional superiority of meat proteins over legume-proteins. No instances of weight loss or anemia in over 100 infants receiving Meat Base Formula were disclosed.

Desirable allergy determinant

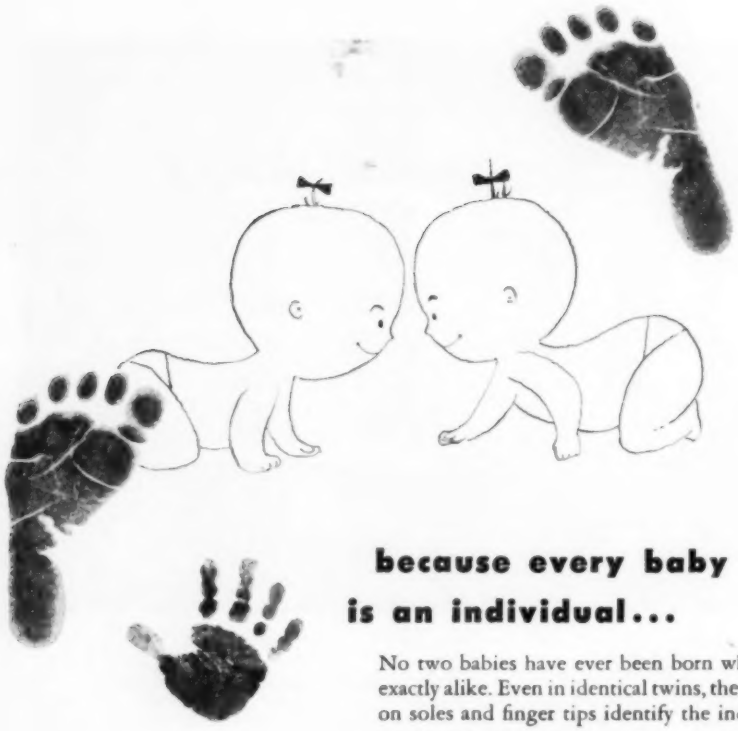
When milk allergy is suspected, replace milk feedings with Gerber Meat Base Formula for 48 to 96 hours. Improvement will confirm diagnosis.

For Meat Base Formula analysis and feeding instruction chart, write to: Dept. of Professional Services, Gerber Baby Foods, Fremont, Michigan.

Babies are our business... our only business!

Gerber®
BABY FOODS
FREMONT, MICHIGAN

**Rowe, Albert, Jr., M.D., and Rowe, Albert H., M.D.: Cal. Med. 81:279 (Oct.) 1954*



because every baby is an individual...

No two babies have ever been born who were exactly alike. Even in identical twins, the tiny whorls on soles and finger tips identify the individual.

So, in infant feeding, the doctor confronts an individual problem each time.

Some years ago, medical research determined that the most satisfactory all-round solution to bottle feeding problems lay in evaporated milk formulae . . . a conclusion borne out by the sure, steady growth of 50,000,000 babies fed evaporated milk.

The flexibility of evaporated milk formulae—which permits the doctor to specify exact carbohydrate needs and alter them, if necessary—is an important reason for this unique success story.

The higher level of protein sufficient to duplicate the growth effect of human milk has been a major factor in the healthy growth of 50,000,000 babies.

And no other formula preparation yet available combines all evaporated milk's major advantages with its great economy.

PET EVAPORATED MILK
is the "going home" formula for more babies than any other form of milk.

PET MILK COMPANY • ARCADE BUILDING • ST. LOUIS 1, MISSOURI

A.M.A. Journal OF
DISEASES of CHILDREN

Incidence of Spina Bifida Occulta in Relation to Age

WATARU W. SUTOW, M.D., Houston, Texas
and
ARTHUR W. PRYDE, M.D., Hiroshima, Japan

With the Statistical Assistance of Marvin A. Kastenbaum, M.S.

INTRODUCTION

During a special roentgenographic survey of the skeletal system in a group of 6- to 7-year-old Japanese children,[1] the incidence of spina bifida occulta was found to be considerably higher than that generally reported in the literature. Spina bifida occulta involving the fifth lumbar and/or the first sacral vertebra was present in 95 (58.3%) of 163 children. The present investigation was undertaken to determine whether or not similar high incidences of neural arch defects existed at older age levels in the Japanese population and to obtain data that may permit evaluation of the relation of age and sex to spina bifida occulta in children.

Submitted for publication Sept. 20, 1955.

From the Laboratories of the Atomic Bomb Casualty Commission, Hiroshima, Japan.

Dr. Sutow is at present at the M. D. Anderson Hospital and Tumor Institute.

This work was sponsored by the Atomic Bomb Casualty Commission, National Academy of Sciences-National Research Council, with funds supplied by the United States Atomic Energy Commission.

MATERIAL AND METHODS

The number and sex of subjects in each age group studied have been summarized in Table 1.

All of these subjects were Japanese who had been residents of Hiroshima City at the time of examination (in 1953). They constituted part of the population sample now under study for late biological effects of exposure to the atomic bomb.

A random sample of women was selected from those in whom the routine diagnostic work included roentgenograms of the pelvic skeleton. Their ages ranged from the middle 20's to the middle 40's.

Data on adult males were obtained from inspection of the spines visible on G-U roentgenograms and scout films of the abdomen. The ages in the adult males ranged from 21 to 67 years, with the great majority between 25 and 45 years.

TABLE 1.—*Spina Bifida Occulta Study*

Age Group, Yr.	Males	Females	Totals
7-8	86	69	155
12	44	51	95
16-18	48	60	108
Adults	79	103	182
	257	283	540

In the children, a single roentgenogram of the lower lumbar spine and sacrum was made for each child with the tube angled cephalad 5 degress and the subject supine on the standard x-ray table. This angle visualized both the lower lumbar spine and sacrum.

The roentgenographic diagnosis of "spina bifida occulta" was made almost without exception only in the presence of a distinct unossified space or gap between the laminae of the neural arch (Fig. 1). Included among spina bifida occulta cases were those very few instances in which definite gaps were not visible on the roentgenogram but in which the appearance of the lines of bony cortex strongly suggested lack of osseous continuity (Fig. 2). Where

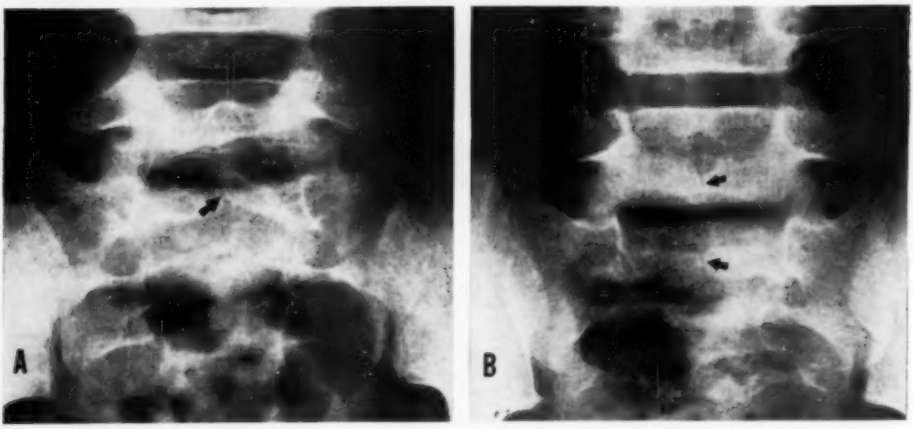


Fig. 1.—*A*, spina bifida occulta is seen in S_1. The edges of the ununited segments of the neural arch are irregular in appearance. *B*, here nonunion is seen in L_5 and S_1. The edges of the ununited segments are regular and even in appearance. With rare exception the cases of spina bifida occulta reported in this series were similar to these two types.

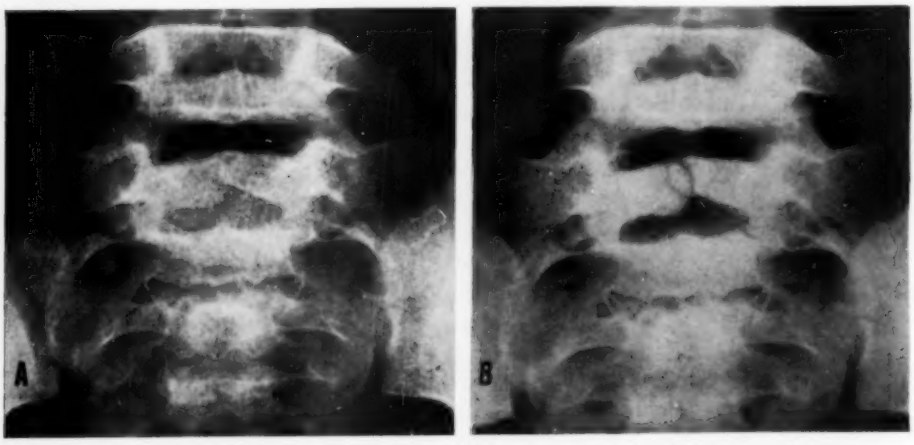


Fig. 2.—*A*, roentgenogram showing a spina bifida occulta of S_1 in which the ununited ends of the neural arch overlap posteriorly and appear closed on a cursory examination. *B*, the same case as *A* retouched to show the defect better. Vertebrae of this type were rare in this series.

TABLE 2.—*Incidence of Spina Bifida Occulta of Fifth Lumbar Vertebra*

Age Group, Yr.	Male			Female			Total		
	No.	w/Defect	%	No.	w/Defect	%	No.	w/Defect	%
7-8	86	19	22.09	69	6	8.70	155	25	16.13
12	44	7	15.91	51	3	5.88	95	10	10.53
16-18	48	6	12.50	60	2	3.33	108	8	7.41
Adults	79	3	3.80	103	1	0.97	182	4	2.20

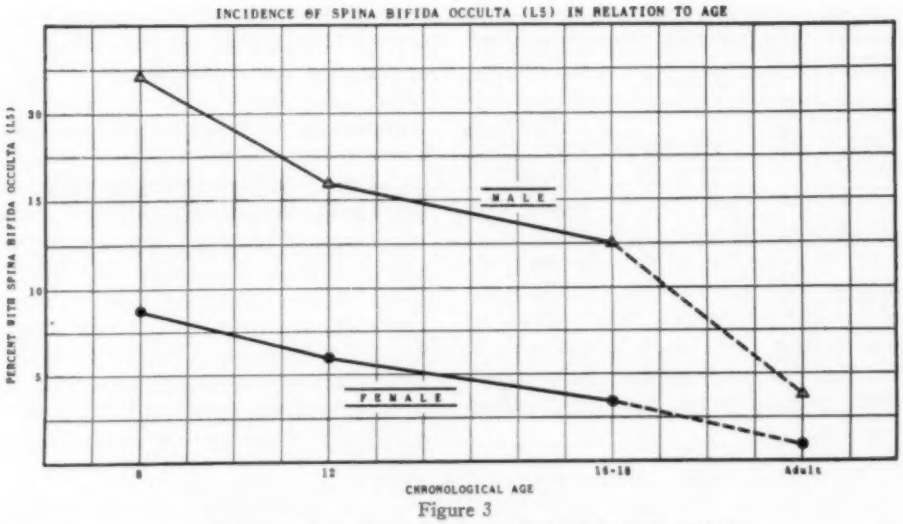


Figure 3

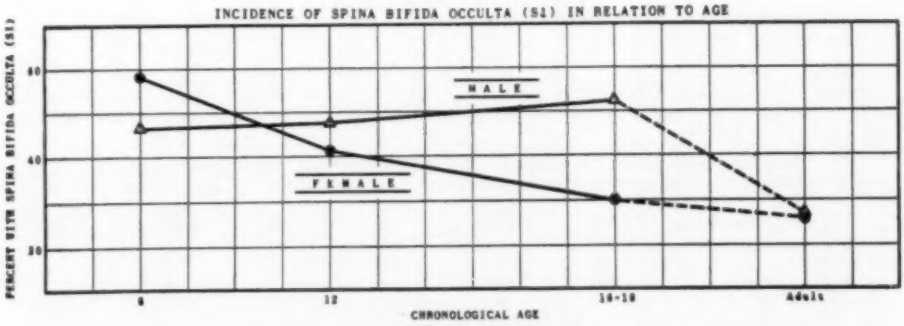


Figure 4

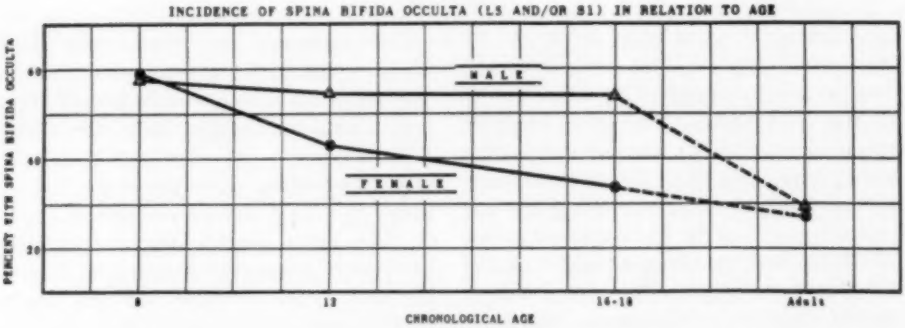


Figure 5

TABLE 3.—*Incidence of Spina Bifida Occulta of First Sacral Vertebra*

Age Group, Yr.	Male No.	Male w/Defect	Male %	Female No.	Female w/Defect	Female %	Total No.	Total w/Defect	Total %
7-8	86	40	46.51	69	40	57.97	155	80	51.61
12	44	21	47.73	51	21	41.18	95	42	44.21
16-18	48	25	52.08	60	18	30.00	108	43	39.81
Adults	79	21	26.58	103	27	26.21	182	48	26.37

detail was not adequate for diagnosis and the patient could not be reexamined, the case was excluded from the series.

RESULTS

1. L_5 Involvement.—Data on the occurrence of spina bifida occulta involving the fifth lumbar vertebra in the various age-sex categories have been summarized in Table 2 and graphically presented in Figure 3.

In the males, the incidence dropped from 22.09% in the 7-8-year-olds to 3.8% in the adults. For the females, the incidence decreased from 8.7% in the 7-8-year-olds to less than 1% in the adults. The incidence among adults when the sexes were combined was 2.2%.

2. S_1 Involvement.—Table 3 summarizes the incidence of spina bifida occulta of the first sacral vertebra. The same data have been graphically presented in Figure 4.

In the 7-8-year-old group, the incidence among girls (57.97%) was higher than that among boys (46.51%). This sex difference was reversed in the 12-year-old group and became marked in the 16-18-year-old group, where the male incidence was 52.08% and the female incidence, 30%. The incidence among adults in both sexes was practically identical, being 26.58% and 26.21%.

3. L_5 and/or S_1 Involvement.—Spina bifida occulta involved both the fifth lumbar and first sacral vertebra simultaneously in a number of patients. Table 4 and Figure 5 show the incidence of neural arch defect in either the fifth lumbar or first sacral vertebra. Table 5 gives the incidence of involvement of both vertebrae at the same time.

Involvement of either of two vertebrae elevated the actual incidence values numerically but did not materially change the shape of the age-incidence curves. At age 7-8 years, the values for both sexes were quite close, being 58.14% for the males and 59.42% for the females. Again, in the adult group, values for the sexes were nearly equal, 29.11% for males and 27.18% for the females. In the other two age groups, however, the incidence values were considerably higher for the males as compared with the females.

TABLE 4.—*Incidence of Spina Bifida Occulta of Fifth Lumbar or First Sacral Vertebra*

Age Group, Yr.	Male No.	Male w/Defect	Male %	Female No.	Female w/Defect	Female %	Total No.	Total w/Defect	Total %
7-8	86	50	58.14	69	41	59.42	155	91	58.71
12	44	24	54.55	51	22	43.14	95	46	48.42
16-18	48	26	54.17	60	20	33.33	108	46	42.59
Adults	79	23	29.11	103	28	27.18	182	51	28.02

TABLE 5.—*Simultaneous Involvement of Fifth Lumbar and Fifth Sacral Vertebra*

Age Group, Yr.	Male No.	Male w/Defect	Male %	Female No.	Female w/Defect	Female %
7-8	86	9	9.55	69	5	7.25
12	44	4	9.09	51	2	3.92
16-18	48	5	10.41	60	0	....
Adults	79	3	3.80	103	1	0.97

COMMENT

1. Incidence.—The incidence of spina bifida occulta in the general population as reported in the literature varies greatly. Data from several sources have been summarized in Table 6.

In an extensive discussion of the subject, Bucy [2] concluded that the probable incidence of spina bifida occulta approximated 5%. Distinction between involvements of the lumbar and sacral vertebrae was not made. Willis [3] reported that nonfusion posteriorly of the neural arch of the fifth lumbar vertebra occurred in 1.2% of 1471 skeletons dissected anatomically. Giles [4] examined 1122 roentgenograms from "negative G-U examinations." He found spina bifida occulta of the last lumbar vertebra in 57 patients and

of the "sacrum" in 227 patients. These figures would give incidences of 5% and 20%, respectively. Giles did not give data on individual vertebrae, and therefore the incidence of spina bifida occulta of the first sacral alone cannot be calculated.

Walker and Bucy [5] reviewed the roentgenograms of spines taken at the University of Chicago over a six-year period and reported only 28 cases (0.3%) with spina bifida occulta of the fifth lumbar vertebra among 7516 cases. In the same study, 113 out of 6945 cases (1.6%) had involvement of the first sacral vertebra.

Karlin [6] roentgenographically examined the spines of 50 "normal" children with children in this series. The inclusion of involvement of first sacral vertebrae also elevated the over-all incidence figures. Thus, the values for incidence of fifth lumbar spina bifida occulta among females were under 9% in the youngest age group and under 1% in the adults. In adult males, the incidence of this same defect was 4%. These values approximated closely some of the figures given by other investigators. On the other hand, the incidence of spina bifida occulta of the first sacral vertebra was exceedingly high, even in the adults. No published data concerning the occurrence of spina bifida occulta in the Japanese could be found to permit any evaluation of racial variations.

TABLE 6.—*Reported Incidences of Spina Bifida Occulta*

Investigator	No. Studied	Material	Ages	Sex M:F	Incidence of Spina Bifida Occulta, %	
					L_5	S_1
Wheeler *	1,000	RG	?	?	2.3	13.1
Sutherland †	12,000	RG	?	2:1	1.17	3.6 (S_1 and S_2)
Willis [3]	1,471	Skeletons	?	M?	1.2	?
Giles [4]	1,122	RG	?	?	5.08	20.23 ("sacrum")
Walker & Bucy [5]	7,516	RG	?	75:48	0.37	....
	6,945	RG	?	75:48	....	1.62
Karlin [6]	50	RG	Children	?	16	44
Lanier [7]	201	Skeleton	Adults	?	0.5	....
Brailsford [8]	3,000	RG	?	?	6	11 (S_1 and S_2)

RG = Roentgenograms.
* Wheeler, T.: Variability in Spinal Column as Regards Defective Neural Arches, cited by Bucy.[5]
† Sutherland, C. G.: A Roentgenographic Study of Developmental Anomalies of the Spine, cited by Bucy.[5]

the purpose of comparing the incidence of spina bifida occulta with that in a group of enuretic children. Of the 50 children, 22, or 44%, had spina fibida occulta of the first sacral and 8, or 16%, had spina bifida occulta of the fifth lumbar vertebra. No age or sex distribution was given. Brailsford,[8] in examining 3000 spines, found defects of the neural arch of the fifth lumbar vertebra in 6% and of the first sacral vertebra in 11%.

These various investigators, therefore, have reported incidence figures which, with the exception of Karlin's study, were considerably below that found in the Japanese during this investigation.

To some extent, age differences may explain the high incidences obtained among

2. Sex and Age Differences.—Statistical analysis of the data, using chi-square tests, indicated significant age and sex differences in the incidence of spina bifida occulta of the fifth lumbar vertebra. When involvement of the first sacral vertebra was considered separately, a highly significant age difference was again found, though no significant difference between males and females was evident. Analysis of the data on the occurrence of either the fifth lumbar or first sacral involvement indicated that significant differences in incidence existed for both age and sex. In general, the data suggested an over-all decrease in incidence with age, as well as a high incidence in the males. No interaction of age and sex was found in any of the three analyses.

Consideration of the fifth lumbar involvement showed a consistently higher incidence for males than for females in all age groups. The difference was most marked in the 7- to 8-year-old group and least marked in the adults. Sex difference was less pronounced, however, when spina bifida occulta of the first sacral vertebra was considered. In the 7- to 8-year-old, 12-year-old, and adult age groups, no sex differences existed. In the 16- to 18-year group, the incidence was significantly higher among the boys.

Change in incidence with age differed with the vertebra involved. Spina bifida occulta of the fifth lumbar segment showed a steady progressive decline in incidence with age. This was true for both sexes. However, a difference in the incidence pattern of the two sexes for first sacral involvement was somewhat apparent. Though this point was not verified by a statistically significant interaction of age and sex, the curve for girls showed progressive decline with increasing age and evidence of a diminishing rate of decrease in incidence after adolescence. For the boys, however, there appeared to be no change in incidence in the 7- to 8-year, 12-year, and 16- to 18-year groups. Between the 16-18-year-old and adult groups, there appeared a sharp drop in incidences.

When data were combined to evaluate the occurrence of spina bifida occulta in either the fifth lumbar or the first sacral vertebra, the resulting incidence curves resembled those of the numerically greater first sacral involvement.

For purposes of comparison, roentgenograms of 95 children, 9 to 10 months of age, were examined. These roentgenograms had been taken during a routine survey for congenital dysplasia of the hips, and in most of them the lumbar vertebrae were satisfactorily visible. In this age group, fusion of the neural arches of the fourth and fifth lumbar vertebrae had occurred in only 25% of the boys and 33% of the girls (Table 7). The unossified gaps in the neural arches in these roentgenograms were indistinguishable in appearance from that to which the term "spina bifida occulta" is applied.

The data obtained in this study, therefore, indicated that the consideration of the two factors, age and sex, was of extreme importance in the evaluation of incidence.

3. Maturational Considerations.—In the course of development of the vertebrae, the two ossification centers for the neural arch extend posteriorly, and fusion occurs in the midline. The time of this fusion varies somewhat in the reports of investigators. Caffey [9] stated that this occurs during the first two years of life. Keith [10] mentioned that the neural arch fuses in the first year. An anatomy textbook [11] generalized that the halves of the arch unite during the first year, union occurring first in the lumbar region and then extending upward. Girdany and Golden [12] have recently revised a composite ossification chart based on recent literature. For the lumbar vertebrae, the fusion of the neural arches was said to occur between the first and seventh year. Hodges [13] indicated that fusion of the arches of the fifth lumbar and first sacral occurs by 5 years of age. These references supported the general impression that fusion of the arches posteriorly occurs relatively early in childhood. As a consequence, spina bifida occulta has been generally accepted as a distinct developmental defect. The possibility that this defect may represent a simple retardation in developmental processes was not usually considered. The consistent decrease in incidence with age and the constant incidence in both sexes among adults in this study were compatible with the concept that spina bifida occulta in some children rep-

TABLE 7.—*Fusion of Neural Arches of Fourth and Fifth Lumbar Vertebrae at Nine to Ten Months of Age*

	Boys	Girls
Fusion completed	13	15
Fusion not completed:		
L_4 only	8	2
L_5 only	13	14
L_4 and L_5	17	13

resented a condition which will eventually disappear as development progresses.

Inspection of the curves presented graphically in Figures 3 to 5 suggested some interesting speculations. It may be possible that, similar to other developmental processes, ossification of the neural arches occurred earlier in girls than in boys. At maturity (adulthood) no difference in the incidence of spina bifida occulta seemed to exist between the two sexes. Variation in time of fusion of laminae of the neural arches appeared to be greater than has been thought. These data also suggested the possibility that such fusion may occur through late childhood and adolescence.

SUMMARY AND CONCLUSIONS

Results of the roentgenographic studies on the occurrence of spina bifida occulta among various age groups in a Japanese population are presented.

Statistical analysis of the data indicates that in the pediatric and adolescent age groups, both sex and age differences exist in the incidence of spina bifida occulta.

Possible significance of these differences in relation to growth and development is considered.

6723 Bertner.

REFERENCES

1. Sutow, W. W., and West, E.: Studies on Nagasaki Children Exposed in Utero to the Atomic Bomb: A Roentgenographic Survey of the Skeletal System, Am. J. Roentgenol. **74**:493, 1955.

2. Bucy, P. C.: Spina Bifida and Associated Malformations, in Brenneman's Practice of Pediatrics, edited by J. McQuarrie, Hagerstown, Md., W. F. Prior Company, Inc., 1948, Vol. 4, Ch. 15.

3. Willis, T. A.: An Analysis of Vertebral Anomalies, Am. J. Surg. **6**:163, 1929.

4. Giles, R. G.: Vertebral Anomalies, Radiology **17**:1262, 1931.

5. Walker, A. E., and Bucy, P. C.: Congenital Dermal Sinuses: A Source of Meningeal Infection and Subdural Abscesses, Brain **57**:401, 1934.

6. Karlin, I. W.: Incidence of Spina Bifida Occulta in Children With and Without Enuresis, Am. J. Dis. Child. **49**:125, 1935.

7. Lanier, R. R.: The Presacral Vertebrae of American White and Negro Males, Am. J. Phys. Anthrop. **25**:341, 1939.

8. Brailsford, J. F.: The Radiology of Bones and Joints, Ed. 5, Baltimore, Williams & Wilkins Company, 1953.

9. Caffey, J.: Pediatric X-Ray Diagnosis, Ed. 2, Chicago, The Year Book Publishers, Inc., 1950.

10. Keith, A.: Human Embryology and Morphology, Ed. 6, Baltimore, Williams & Wilkins Company, 1948.

11. Gray, H.: Anatomy of the Human Body, edited by W. H. Lewis, Ed. 24, Philadelphia, Lea & Febiger, 1942.

12. Girdany, B. R., and Golden, R.: Centers of Ossification of the Skeleton, Am. J. Roentgenol. **68**: 922, 1952.

13. Hodges, P. C.: An Epiphyseal Chart, Am. J. Roentgenol. **30**:809, 1933.

The Simultaneous Occurrence of Leukemia and Mongolism

Report of Four Cases

WILLIAM KRIVIT, M.D.
and
ROBERT A. GOOD, M.D., Minneapolis

In the course of clinical studies on acute leukemia in childhood, the rare combination of leukemia and Mongolism was noted in four children during a one-year period. In each patient the somatic stigmata of Mongolism were classical, and the diagnosis of leukemia was confirmed on bone-marrow aspiration.

A single case of combined acute leukemia and Mongolism would be remarkable, considering the rarity of each of the two conditions and the consequent unlikelihood of their occurring together by chance. For example, Mongolism occurs no more frequently than once per 500 live births.[1] Leukemia in the 0- to 4-year age range is present in about 5/100,000 respective population.[2] Thus the expected occurrence of the leukemia-Mongolism combination by chance alone in children 0-4 years of age would be 1/10,000,000, an experience to be anticipated in Minnesota once in 50 to 100 years at the present Minnesota birth rate. Thus when four cases were observed within one year, the possibility of coincident occurrence by chance alone seemed remote.

An extensive search through the literature, however, revealed that only two similar cases have been reported. Schunk and Lehman [3] and Bernhard and co-workers [4] each described one infant having both leukemia and Mongolism. Bernhard mentioned that Farber * had observed similar cases in Boston, and informal personal communication with other centers indicates that several other instances of this double disaster have been observed but not reported. It may be that the paucity of literature on this subject does not indicate the true incidence of the combination of these two diseases. Recently Bernard and co-workers [5] have described three additional cases of leukemia occurring together with Mongolism in infancy.

The establishment of the occurrence of Mongolism and leukemia in combination in a frequency considerably greater than that expected by chance might well be provocative of considerations which could shed light on the essential nature of either or both of these diseases. It is with the hope of stimulating such considerations as well as future reporting of this combination of diseases that the following four case reports are submitted.

CASE 1.—A 2-year-old girl became ill 10 weeks before admission. The illness consisted of pain on movement of the right hip and left shoulder. Fever, anorexia, and pallor were also noted. Six weeks before admission the diagnosis of leukemia was made by morphologic studies of the peripheral blood.

Submitted for publication Sept. 19, 1955.

From the Department of Pediatrics, University of Minnesota Medical School, and the Research Laboratories of the Variety Club Heart Hospital.

This study was aided by grants from the Minnesota Division of the American Cancer Society and the American Cancer Society.

American Legion Memorial Heart Research Professor of Pediatrics (Dr. Good).

* In a recent personal communication to one of us Farber states that he has observed six cases of coincident Mongolism and leukemia.

Therapy consisted of several whole-blood transfusions and prophylactic antibiotic therapy. Because of the continued pain and because of the onset of hematemesis the patient was transferred to our hospital for further care.

The typical features of Mongolism which were present at birth included narrowing of the palpebral fissures, marked epicanthal folds, flattened nasal bridge, protruding tongue, hyporeflexia, and increased laxity of the joints. Slow intellectual and motor development had been observed. The mother had been 42 years old at birth of the child but gave no history of illness, injury, or deprivation during the pregnancy, and no abnormalities were known to have attended labor.

Physical Examination.—Weight 9.9 kg., height 86 cm. Both the liver and the spleen were palpable. Firm nodes were palpable in the neck, axillary, and inguinal areas. Petechiae and ecchymosis were present on the skin and mucous membranes.

X-Ray Examination.—A destructive process involving the head of the left humerus and the neck of the right femur was revealed. This was thought to be indicative of malignant infiltration and compatible with the diagnosis of leukemia.

Laboratory Findings.—Hemoglobin was 4.7 gm/100 cc. White blood cell count was 2800, with a differential count of 25% neutrophiles, 69% lymphocytes, 6% monocytes. Platelets were 22,000. Bone-marrow biopsy revealed the marrow to be hypocellular, to contain numerous immature cells, and to be compatible with a diagnosis of acute leukemia.

The therapy consisted of transfusions when necessary and symptomatic care of the pain in the hip and shoulder. Following establishment of the diagnosis a spontaneous remission occurred, and for a period of 10 months the child required no further aid and was asymptomatic. However, thereafter the disease recurred and the child then had a progressively downhill course. She required frequent transfusions. Hemorrhagic tendency associated with a low platelet count again presented a problem. Generalized adenopathy and hepatosplenomegaly recurred. Bone-marrow examination demonstrated consistent hypocellularity and infiltration with leukemic cells. Finally, after repeated transfusions, the patient died, on March 1, 1955. Autopsy permission was not obtained.

CASE 2.—Six months prior to admission a 2-year-old white girl developed an upper respiratory infection and thereafter became progressively weak and pale. She was admitted to the Minneapolis General Hospital, where a diagnosis of acute lymphatic leukemia was make on clinical grounds and confirmed by bone-marrow examination. On therapy with amethopterin, 6-mercaptopurin, and cortisone, a remission occurred. During the remission the child was kept on prophylactic antibiotic therapy. Readmission was necessary three months later because of return of fever and pain and because of an increasing peripheral white cell count. She was again treated with antileukemic therapy with fair response. Another admission was necessary on June 14, 1954, because of hematemesis and purpura. Her condition became critical, and she was transferred to the University of Minnesota Hospital for management.

The mother was 39 years old at birth of the patient. The birth and neonatal periods were uneventful. The diagnosis of Mongolism had been made by several doctors during the first three years of life. At the age of 3 years she was obviously retarded and could say only a few words. She began to walk when she was approximately 2 years old.

Physical examination revealed a child who had a Mongoloid facies, with marked epicanthal folds, small palpebral fissures, and a protruding tongue. Her weight was 15 kg.

The leukemic process was evidenced clinically by the presence of generalized adenopathy, marked hepatomegaly, and generalized purpura.

Bone marrow aspiration revealed that 85% of the marrow cells were immature lymphoid cells, lymphoblasts, and damaged immature lymphoid cells. The morphological diagnosis was subacute lymphatic leukemia.

The child was given 100 mg. of cortisone per day, 2.5 mg. of amethopterin per day, potassium chloride, oxytetracycline (Terramycin), and repeated blood transfusions. The white cell count fell from 1500 to 400, and the child died on July 5, 1954, with generalized gastrointestinal hemorrhage, hematemesis, and pneumonia.

Autopsy revealed evidence of subacute lymphatic leukemia with involvement of liver, spleen, kidneys, and lymph nodes. The liver weighed 400 gm. and the spleen 100 gm. A high interventricular septal defect was also found.

CASE 3.—A 3-day-old boy was admitted to the University of Minnesota Hospitals for the first time because of numerous hemorrhagic spots on the face and scalp and a redundancy of the skin of the face and neck.

Birth weight was 10 lb. 6 oz. (4706 gm.). Because of the persistence of the petechiae and ecchymosis, the occurrence of jaundice, the generalized puffiness of the skin, and the remarkable lethargy, the patient was referred to the University of Minnesota Hospitals.

On physical examination the infant appeared lethargic. Weight 4100 gm., height 55 cm. Numerous ecchymotic spots were present over the face, forehead, and scalp. Swelling of the right upper eyelid was evident. The spleen was palpable 4 cm. below the left costal margin. The liver was palpable 3 cm. below the right costal margin.

During the next several weeks as the edema subsided, it became apparent that there were marked epicanthal folds and that the child had typical Mongoloid facies. The characteristic hyporeflexia and relaxation of the ligaments and joints were also better appreciated after the edema diminished.

About two weeks after admission a bone-marrow examination was done, which was diagnostic of subacute lymphatic leukemia. The bone-marrow differential count was as follows: lymphoblasts 18.6%, immature lymphocytes 14.6%, lymphocytes 21.4%, monocytes 22%, plasma cells 1%, normoblasts 3.4%, myeloid cells 19.0%.

After this diagnosis the child was placed on therapy with cortisone and amethopterin and a clinical remission ensued.

The bone marrow on June 9, 1954, demonstrated complete hematological remission. The child was followed in the outpatient department and treated with cortisone, potassium chloride, and benzathine penicillin (Bicillin).

Approximately two months later the infant was readmitted to the University Hospitals because of recurrence of the petechiae, lymphadenopathy, hepatosplenomegaly, and a peripheral white cell count of 130,000, with 95% immature lymphocytes and lymphoblasts. Despite therapy the child continued a progressively downhill course and suddenly died after receiving two transfusions of whole blood. Death was thought to be due to generalized hemorrhage and pneumonia. Permission for autopsy was not obtained.

After the above three cases had been observed and this paper describing the Mongolism-leukemia syndrome had been drafted, a Mongoloid child was born in our hospital. Because the child was doing poorly and because we were sensitized by this study to the combined occurrence of leukemia and Mongolism, hematological investigation was performed on this infant. It was found that the baby was suffering from leukemia in which the differentiation of cells was primarily along the myeloid line.

CASE 4.—A baby boy was born to a 21-year-old mother following a normal pregnancy terminated by a normal labor and delivery. On the first physical examination it was noted that the baby possessed the classical somatic features of Mongolism. He was brachycephalic, had narrow palpebral fissures, marked epicanthal folds, a prominent tongue, poorly developed nasal bridge, and small medially deviated fifth digit. The baby lacked vigor and was very flaccid. Physical examination revealed no other evidence of abnormality.

The infant developed an erythematous vesicular rash over the chest and face. The possibility that the child might have neonatal leukemia was considered, and hematological examination was begun. The hemoglobin initially was normal at 17.0 gm. per 100 cc. The white blood cell count was 32,000/cubic millimeter and the platelet count 56,000/cubic millimeter. Morphological study of the peripheral blood revealed 23.5% blasts, 23% immature reticular cells, 26.5% neutrophiles, 25% lymphocytes, and 2% monocytes. A diagnosis of congenital leukemia was made. Bone marrow was obtained, and the morphological diagnosis was subacute leukemia with development primarily along myeloid lines. It was the opinion of the hematologist that the form of the leukemia was best described as leukemic reticuloendotheliosis of Downey.

At the time of writing the child has lived approximately three weeks, with progressive development of anemia and thrombocytopenic purpura. The leukemia in the peripheral blood and bone marrow has persisted. In addition the baby has developed progressive hepatosplenomegaly and lymphadenopathy.

It is to be emphasized that in this baby the diagnosis of leukemia was made because of the high index of suspicion fostered by the cases reported in this paper. The blood and bone-marrow studies which established the diagnosis of neonatal leukemia were made only because this was a Mongoloid infant who failed to do well in the neonatal period.

COMMENT

The occurrence of four cases of leukemia in Mongoloid children represents a provocative observation. This experience cannot be a function of the special attention paid to either Mongolism or leukemia in our clinic. Our observation of these several cases of associated leukemia and Mongolism must be taken to suggest that some biologic relationship between the two diseases exists.

What the relationship might be is not clear, but several possibilities suggest themselves. It is possible that leukemia and Mongolism can be the function of a single teratogenic force operating during the sixth to the ninth week of pregnancy. This period is suggested in Ingalls'[1] observation that all the defects characteristic of Mongolism occur in tissues undergoing rapid differentiation during this time. In addition, the earliest phase of endogenous organ hematopoiesis, hepatic hematopoiesis, is just beginning during this gesta-

tional interval.[6] The possibility that either an endogenous or exogenous toxic factor could induce changes responsible for both the leukemia and Mongolism by exerting an effect at this critical time seems real.

The early studies of Bittner [7] and Rous [8] provoked investigations which have shown that many different kinds of cancer in animals may be due to infection with filterable viruses.† Similarly, the recent work of Gross [11] has extended this concept to include experimental leukemia in mice. Finally, Magrassi,[12] in an unconfirmed report, has even claimed that human leukemia may be transmitted to the guinea pig by a filterable agent. These observations provide basis for thought with respect to the relationships involved in the simultaneous occurrence of Mongolism and leukemia. It may be, for example that in certain patients invasion by a leukemia-producing agent occurs in some instances during the critical period of organogenesis and results in damage sufficiently widespread to cause the somatic and neural stigmata of Mongolism. The occurrence of congenital leukemia in two of our cases and its observation in other reported cases ‡ of the Mongolism-leukemia syndrome would be compatible with this suggestion.

The discrepancy between the frequency of the leukemia-Mongolism syndrome suggested by our study and that indicated by review of the literature deserves consideration. Although it may be that our experiences represent mere fortuity, other possibilities exist. The paucity of case reports may reflect the reluctance of physicians to perform traumatic diagnostic procedures, such as bone marrow aspiration, on Mongoloid children. Another possible explanation for the difference might be that antibiotics have permitted prolonged survival of the Mongoloid children, providing more opportunity for development of leukemia in a susceptible population. But to us the possibility which seems most likely is that heretofore physicians diagnosing combined leukemia and Mongolism could find no reason for reporting their observations.

† References 9 and 10.

‡ References 3 and 4.

Consideration of the joint occurrence of leukemia and Mongolism as an "experiment of nature" which might well elucidate mechanisms responsible for either or both of these diseases might stimulate additional reports of the combined disorder.

SUMMARY

Four cases of combined Mongolism and leukemia are reported.

The consideration that the combination of these diseases did not occur by chance is submitted.

Possible biologic relationships between the two diseases are considered.

Reporting of the coexistence of leukemia and Mongolism is urged.

ADDENUM

While this paper was in press an additional case of combined leukemia and mongolism was discovered. The observations on this patient follow.

CASE 5.—A known Mongoloid 2½-year-old child was admitted to the University of Minnesota Hospitals for diagnosis of anemia and fever. Intermitttently since December, 1955, she had temperatures ranging to 104 F. Lethargy, generalized weakness, and inability to walk were noted in succession. On Jan. 4, 1956, anemia was noted by the physician. She received iron therapy and two blood transfusions and was transferred to the University of Minnesota Hospital.

The pregnancy and delivery were uncomplicated. The mother was aged 46 years and had four other normal children, who are alive and well.

The physical examination demonstrated classical stigmata of Mongolism, including the following: marked epicanthic folds, flattening of the nasal bridge, marked muscular and joint hypotonia, flattening of the occiput. Mental retardation was also noted. Lymphadenopathy was present in the inguinal, axillary, and cervical areas. The liver was palpable 2 cm. below the costal margin.

Hemoglobin was 9.3 gm. per 100 cc., and platelets numbered 90,000. Examination of the peripheral blood revealed no neutrophiles, and the total count was 1300/cu. mm. The presence of numerous blasts in the peripheral blood supported the diagnosis of acute leukemia. Bone marrow smears and imprints of the lymph node biopsy revealed findings diagnostic of acute lymphatic leukemia.

The observation of this case of combined Mongolism and leukemia while this paper

was in press supports the conclusion drawn in the paper that the relation between these two diseases is an essential one deserving of detailed consideration.

REFERENCES

1. Ingalls, T. H.: Etiology of Mongolism: Epidemiologic and Teratologic Implications, Am. J. Dis. Child. **74**:147-165, 1947.

2. Cooke, J. V.: Occurrence of Leukemia, Blood **9**:340-347, 1954.

3. Schunk, G. J., and Lehman, W. L.: Mongolism and Congenital Leukemia, J. A. M. A. **155**: 250-251, 1954.

4. Bernhard, W. G.; Gore, I., and Kilby, R. A.: Congenital Leukemia, Blood **6**:990-1001, 1951.

5. Bernard, J.; Mathie, S., and Bernoud: Leukemia in Infants, Arch. franç. pédiat. **11**:470-502, 1955.

6. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1951.

7. Bittner, J. J.: Inciting Influences on the Etiology of Mammary Cancer in Mice, in A. A. A. S. Research Conference on Cancer: A Conference of Papers and Discussions Presented at the Summer Meeting of the Section on Chemistry of the American Association for the Advancement of Science, at Gibson Island, Maryland, July 31-August 4, 1944, edited by F. R. Moulton, Washington, D. C., American Association for the Advancement of Science, 1946, pp. 63-96.

8. Rous, P.: Transmission of a Malignant New Growth by Means of a Cell-Free Filtrate, J. A. M. A. **56**:198, 1911.

9. Shrigley, E. W.: Virus-Induced Tumors of Animals, Ann. Rev. Microbiol. **5**:241-264, 1951.

10. Viruses as Causative Agents in Cancer, Ann. New York Acad. Sc. **54**:869-1232, 1951.

11. Gross, L.: Is Leukemia Caused by a Transmissible Virus, Blood **9**:551-573, 1954.

12. Magrassi, F.: Latent Infections and Infectious Virus Diseases in Relation to the Etiopathogenetic Problem of Leukemia, Minerva med. **44**:1957-1962, 1953.

News and Comment

ANNOUNCEMENTS

Summer Camp for Diabetic Children.—A summer camp for diabetic children will be opened for the eighth season under the auspices of the Chicago Diabetes Association, Inc., from July 15 to Aug. 5, 1956, at Holiday Home, Lake Geneva, Wis.

In addition to the complete camp personnel, the Chicago Diabetes Association furnishes a staff of resident physicians and dietitians, trained in the care of diabetic children.

Boys and girls ages 8 through 14 years are eligible. For further information regarding fees, interested persons should be directed to write or phone the office of the Chicago Diabetes Association. Fees will be set on a sliding scale to meet individual circumstances.

Physicians are urged to notify parents of diabetic children and to enter the names of children who would like to attend camp. Applications may be obtained from and inquiries should be addressed to: The Chicago Diabetes Association, 5 S. Wabash Ave., Chicago 3. Phone: ANdover 3-1861.

Limited capacity requires prompt application.

Postgraduate Courses in Pediatrics.—Two postgraduate courses in pediatrics are being offered by the Department of Pediatrics, Harvard Medical School, at Massachusetts General Hospital, in June, 1956. The first, which will be from June 11 through 19, will deal with general pediatric problems exclusive of endocrine and metabolic disorders. The second, June 20 through 22, will deal specifically with parenteral fluid therapy, management of nephritis and nephrosis, diabetes, disturbances of growth, and related endocrine disorders in children and adolescents. Enrollment may be for either course or the total combined course. Those interested should write Courses for Graduates, Harvard Medical School, 25 Shattuck St., Boston.

Meconium Ileus

A Clinical Study of Twenty Surviving Patients

HARRY SHWACHMAN, M.D.
CHARLES V. PRYLES, M.D.
and
ROBERT E. GROSS, M.D., Boston

INTRODUCTION

Meconium ileus refers to intestinal obstruction in the newborn infant by abnormal, thick, tenacious meconium. This type of obstruction accounts for approximately 15% of all types encountered in the neonatal period. The usual site of the obstruction is the terminal ileum, which may be greatly distended and hypertrophied. The length of ileum plugged with meconium may vary from a few centimeters to over 3 ft. Late recognition of this condition, with the development of serious complications, such as intestinal perforation with meconium peritonitis, gangrene of the intestine, and aspiration pneumonia, explains the high mortality rate in the past. Prior to 1945, almost all infants with meconium ileus died, although rare instances of recovery have been reported.[1] The few infants who survived surgery in the neonatal period died later in infancy with an obstructive and suppurative pulmonary process; this latter represents another serious manifestation of the generalized disease of which meconium ileus may be the initial manifestation. With increasing knowledge and earlier recognition of the condition and improved surgical techniques and postoperative care a number of patients have been treated successfully.*

The purpose of this paper is to report on the course and present status of 15 infants successfully relieved of their obstruction by surgical means and who are still living as of July, 1955. In addition, five infants with intestinal obstruction in the newborn period who did not require surgical intervention and who later developed cystic fibrosis of the pancreas will be included. These patients presumably had meconium obstruction of a mild degree and responded to conservative medical treatment.

HISTORICAL REVIEW

Reference to meconium ileus was made by Landsteiner, in 1905,[6] in a report of the autopsy findings in one patient. He concluded that the lesion of the pancreas was responsible for the intestinal obstruction caused by the abnormal meconium. He also referred to another case of obstruction due to thickened meconium, and in this case the pancreas was normal but there was no secretion of bile. He felt that both bile and pancreatic juice might be necessary for the formation of meconium of normal consistency. This

Submitted for publication Sept. 22, 1955.

From the Division of Clinical Laboratories and the Departments of Medicine and Surgery, Children's Medical Center, and the Department of Pediatrics, Harvard Medical School.

This work was supported in part by Research Grant A-80 from The National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, U. S. Public Health Service, and by the Sharples Fund.

Assistant Professor of Pediatrics, Harvard Medical School, and Chief, Division of Clinical Laboratories, Children's Medical Center (Dr. Shwachman); formerly Chief Resident, Medical Out-Patient Department, Children's Medical Center, Assistant Professor of Pediatrics, Boston University School of Medicine, and Research Associate, Thorndike Laboratories, Boston City Hospital (Dr. Pryles); William E. Ladd Professor of Children's Surgery, Harvard Medical School, and Chief of Surgical Service, Children's Medical Center (Dr. Gross).

* References 2-5.

view was shared by Dodd,[7] who reported on one case of meconium ileus and reviewed five others in which complete postmortem examinations had been made. She felt that failure of pancreatic secretion or bile to reach the gastrointestinal tract during fetal and neonatal life is part of the cause of meconium ileus. Kornblith and Otani [8] and Hurwitt and Arnheim,[9] in two separate reports, each of one case, claimed that congenital stenosis of the pancreatic ducts could be responsible for meconium ileus. These cases are rare and require painstaking examination with serial sections to demonstrate the obstruction in the pancreatic ducts. In the excellent study of Hurwitt and Arnheim, over 500 sections of the pancreas taken 8μ apart were made. In their study of the normal development of the pancreatic duct, they obtained authoritative views from G. Streeter and J. L. Bremer. The pancreatic ducts do not pass through a period of occlusion by epithelial proliferation such as has been described in the biliary system and duodenum. Hurwitt and Arnheim felt that their case was due to a focal developmental defect. Perhaps one might consider the obstruction secondary to the scarring that takes place in pancreatic fibrosis rather than due to a primary congenital atresia.

The association of meconium ileus with pancreatic achylia was shown by Andersen [10] and Farber.[11] In 1938, Andersen reported the similarity between the histological appearance of the pancreas in cases of meconium ileus and cystic fibrosis of the pancreas and contended that the former was merely an early manifestation of the latter. Farber showed the relationship of the pancreatic lesion with its resultant defective enzyme production to the altered physical state of meconium. The meconium was described as unusually tenacious and tarry and very difficult to remove. In 18 infants who died of intestinal obstruction caused by inspissated meconium, Farber found pancreatic changes which were characterized by inspissation of secretions, dilatation of the ducts, atrophy of the acini, and interstitial fibrosis. Congenital stenosis of the pancreatic ducts was not claimed for any of these cases. Farber postulated that the survivors of meconium ileus would eventually develop the clinical picture of cystic fibrosis as seen in older infants and children. The development of this clinical sequence was reported in four patients by May and Lowe,[12] in 1949. Three of these patients with meconium ileus died in infancy but lived sufficiently long to develop characteristic pulmonary symptoms. The fourth patient, who was 6 years of age at the time of their report, is Patient 16 in our present series. The oldest survivor of meconium obstruction treated surgically is an 18-year-old boy reported by Lips and Wiebenga.[1] This patient developed the clinical manifestations of cystic fibrosis of the pancreas. He also had bronchiectasis and mild diabetes mellitus. Pancreatic insufficiency was demonstrated by examination of the duodenal fluid, with the finding of absent trypsin, lipase, and amylase with an increase in viscosity.

Glanzmann [13] suggested that the inspissation of meconium in meconium ileus might be due to obstructing mucus secretions from the intestines and not to lack of pancreatic enzymes. Bodian [14] stated that the excessive viscidity of the meconium which is composed largely of abnormal mucus leads to inspissation and obstruction. He felt that it was unlikely that the absence of pancreatic enzymes had more than a contributing effect and stated that other pancreatic malformations associated with lack of enzymes during fetal life do not lead to meconium ileus. Denzer,[15] in a case report, noted mild lesions of the pancreas in an infant dying following operation for meconium obstruction. He stated that the severity of the disturbance may be out of all proportion to the degree of demonstrable organic change in the pancreas. Zuelzer and Newton [16] found a pancreatic lesion of moderate severity in four patients with meconium ileus and advanced changes in a fifth case in which they felt organic atresia was present. Extrapancreatic changes were inconspicuous and confined to the alimentary tract in these five patients who died in the newborn period.

Buchanan and Rapaport † concluded that the meconium in meconium ileus is an abnormal secretory product of the intestinal and gastric glands. The finding of small amounts of purine and phosphorus in normal meconium does not support the previously held theory that meconium was formed as a result of the accumulation of the cytoplasmic cellular residue and nuclei of desquamated cells from the gastrointestinal tract during fetal development. These investigators compared the chemical composition of normal pooled meconium with that derived from a patient with meconium ileus. Striking differences, both quantitative and qualitative, were found between the two types of meconium. A larger volume of meconium was noted in the patient with meconium ileus. The most prominent component of normal meconium appeared to be a polysaccharide which yielded a reducing sugar after acid hydrolysis. The meconium from the patient contained less carbohydrate and more nitrogen and reacted like a protein in its precipitation reactions. It also contained a heat-coagulable material. Of interest is the behavior of pepsin, which showed considerable digestion of meconium from the meconium ileus patient with relatively little action on normal meconium. Under the conditions of the experiment trypsin showed less activity than pepsin on either normal meconium or that from the patient with meconium ileus. The increased viscidity of the abnormal meconium was attributed to its higher mucoprotein content. Glanzmann and Berger [19] had previously studied the chemical composition of meconium from patients with meconium ileus and demonstrated the presence of an abnormal protein which formed a gel-like mass with lipids.

The observation that meconium from patients with meconium ileus can be readily digested by pancreatic enzymes and by normal duodenal fluid was shown in Farber's laboratory by one of us.[11] It appears that the production of an excessive amount of abnormal meconium by the gastrointestinal glands in association with pancreatic achylia leads to meconium ileus.

† References 17 and 18.

CASE MATERIAL

The 20 patients included in this study are selected because they are living as of July 1, 1955. Fifteen of these patients were treated surgically. Five patients (Patients 16-20) were relieved of their obstruction by nonsurgical means and later developed evidence of pancreatic insufficiency.

A summary of the essential data from each of the 15 patients with meconium ileus requiring surgery is given in Table 1. The oldest patient is now 8½ years of age. There are eight boys and seven girls, all of the Caucasian race. None were born prematurely. The birth weights varied from 5 lb. 5 oz. to 8 lb. and 6 oz. These infants were admitted to the surgical service at from 1 to 4 days of age with symptoms and signs of intestinal obstruction. The initial x-ray examination of the abdomen showed marked gaseous distention of the bowel, with what appeared to be bubbles of air in the meconium; the distal colon was not visualized as a rule. In only two cases were fluid levels seen in segments of the small bowel. Pneumoperitoneum and free meconium in the peritoneal cavity were seen radiologically prior to operation in Cases 1 and 4. The type of operation in the majority of cases was a Mikulicz resection with a double-barrel ileoileostomy. Closure of the ileostomy was accomplished in approximately two to three weeks in most cases. In Patient 1, the transverse colon was perforated and generalized peritonitis was present. The initial operation consisted of a resection of distal ileum, cecum, appendix, and ascending colon and Mikulicz ileocolostomy. The closure was not effected until 11 months of age. In Patient 4 the sigmoid colon was perforated and there was free meconium in the peritoneal cavity at the time of operation. Closure in this patient was accomplished at seven months, at which time an end-to-end anastomosis of the sigmoid colon was performed. In nine patients a segment of bowel varying in length from 0.9 to 55.0 cm. was removed. The average duration of hospitalization for the surgically treated infants was 30 days; the shortest stay was 15 days, for Patient 11, and the longest was 51 days, for Patient 15. After discharge from the hospital the medical management in most cases was closely supervised in the Nutrition Clinic or in our private office.

Infants admitted to the hospital in the newborn period with intestinal obstruction which was relieved by medical means, that is, enemas, gastric lavage, instillation of pancreatic enzymes, are listed in Table 2; all of these infants later developed evidences of cystic fibrosis. The nature and significance of the obstruction was appreciated at the time of hospital study. This is reflected in attempts at duodenal intubation in three of these patients at an

TABLE 1.—*Summary of Cases of Meconium*

Patient	Birth Date	Sex	Birth Weight, Lb.-Oz.	Age at Operation, Days	Type of Operation	Days in Hospital	Discharge Weight, Lb.-Oz.	Duodenal Intubation	
								Age	Results
1	1/21/47	M	7-3	2	Mikuliez ileocolostomy 1/23/47; closure 12/31/47	37	6-14	11 mo.	Neg. for trypsin
2	2/10/48	F	7-3	3	Mikuliez ileoileostomy	30	6-14	23 days	Fluid scant; neg. for trypsin
3	6/4/49	M	7-9	36 hr.	Mikuliez ileoileostomy	36	7-8½	1 mo.	Too viscid to measure viscosity; neg. for trypsin
4	7/28/49	M	6-2	3	Exteriorization at perforated sigmoid 7/31/49; closure 2/15/50	18	6	15 days	Increased viscosity; neg. for trypsin
5	2/23/50	F	6-3	2	Mikuliez ileoileostomy	22	5-12	12 days	Scant viscid fluid; neg. for trypsin
6	5/18/50	F	5-8	3	Mikuliez ileoileostomy	22	5-3	3 wk.	Scant, viscid; neg. for trypsin
7	2/8/51	M	7-9	3	Mikuliez ileoileostomy	19	7-7	15 days	Fluid viscid; neg. for trypsin
8	9/13/51	M	5-5	5	Mikuliez ileoileostomy	43	7-11	40 days	Trypsin absent
9	6/30/52	F	6-1¼	2	Mikuliez ileoileostomy	35	6-4	Not done	.....
10	10/13/52	F	5-9	1	Mikuliez	20	5-12	1 yr.	Scanty viscid fluid; amylase, lipase, trypsin absent
11	12/14/52	M	6-13	1	Mikuliez ileoileostomy	15	6-11	7 mo.	Scant fluid insufficient for testing
12	12/15/52	F	5-10	2	Resection of strangulated bowel; end-to-end anastomosis*; abdominal exploration on 12/21/52; ileostomy	31	6-8	Not done	.....
13	11/27/53	M	6-13	3	Mikuliez ileoileostomy	47	6-12	1 mo.	Amylase, lipase, trypsin absent
14	4/15/54	F	6-9	2	Mikuliez ileoileostomy	31	5-13½	1 mo.	Proteolytic activity approx. 1/5 normal; lipase ½ normal
15	1/2/55	..	8-6	3	Mikuliez ileoileostomy	31	7-15	Not done	.....
Re-admitted 3/4-3/13					Obstruction with fecal impaction	..	....	.....	.....

* Operation performed at Mercy Hospital, Portland, Maine.
† C indicates continuous; I, intermittent.

early age (2 days, 6 days, and 2 weeks). The clinical course and laboratory findings are similar in every respect to the patients listed in Table 1.

CLINICAL MANAGEMENT

The surgical management of our patients with meconium ileus is recorded in detail.[3] Following successful surgery the important problems are concerned with attempts to maintain nutrition and to prevent the early onset of pulmonary manifestations. In general, therapy in this group of patients is similar to that previously described for patients with cystic fibrosis in whom the disease is detected months or even years after birth.[20]

In the management of the nutrition of infants with meconium ileus an adequate caloric intake is provided. Approximately 90 to 100 Cal. per pound of body weight per day is offered during the first few months of life. To satisfy the appetite of these hungry infants a three-hourly feeding schedule is recommended. The composition of the formula is relatively low in fat, with a liberal allowance of carbohydrate and protein. The fat intake is limited primarily because a generous amount, that is, over 50 gm., may result in large, frequent, fatty bowel movements and discomfort to the patient. The protein content of the diet is approximately

Ileus with Surgical Correction

Sweat Electrolytes, mEq./L.		Onset Pulmonary Symptoms	Current Chest Findings by X-Ray	Age Antibiotics Begun	Present Status (July, 1955)			
Age, Yr.	Na	Cl				Antibiotics†	Pancreatin†	Nutritional (Weight Percentile)	Pulmonary
[a] 5/12	83.5	99.0	1 mo.	Emphysema; increased bronchovascular markings; minimal atelectasis	10 mo.	I	I	35	Mild
6 9/12	107.6	107.5	1 mo.	Emphysema; diffuse peribronchial inflammation; clouding of antra and ethmoids	6 mo.	C	I	25	Moderate to severe
5 5/12	75.4	78.8	11 wk.	Irregular aeration	2 days	C	I	35	Moderate
6 0/12	136.2	138.4	2 mo.	Slight prominence of bronchovascular markings; hyperaeration and irregular aeration	2 wk.	C	C except for period 11/9/50-3/15/51	60	Mild
8 8/12	84.4	88.6	1 mo.	Emphysema; irregular aeration; increased bronchovascular markings	2 days	I	I	50	Mild
5 6/12	130.0	129.8	6 wk.	Normal	2 days	C	I	<3	Normal
3 8/12	98.2	123.0	6 wk.	Emphysema; irregular aeration; atelectasis—right middle lobe	4 days	C	I	50	Severe
3 0/12	150.0	190.0	1½ mo.	Irregular aeration; marked emphysema; lobular atelectasis	4 days	C	C	<3	Severe
2 11/12	108.4	97.0	2 wk.	Irregular aeration with emphysema; focal atelectasis	2 days	C	C	<3	Moderate to severe
3 5/12	104.0	108.5	7 wk.	Moderate hyperaeration with increased bronchovascular markings	2 days	I	C	20	Mild
2 2/12	133.7	122.1	None	Normal	2 days	C	C	90	Normal
2 5/12	131.6	114.2	1 mo.	Emphysema bilaterally with irregular aeration	2 days	C	I	<3	Moderate
1 7/12	109.7	118.2	1 mo.	Emphysema bilaterally with irregular aeration	3 days	C	C	10	Moderate
1 3/12	123.2	126.9	Approx. 2 wk.	Emphysema, irregular aeration, atelectasis	3 days	C	C	10	Moderate
6/12	90.5	98.3	2 wk.	Irregular emphysema; peribronchial thickening	3 days	C	C	25	Moderate
.....	.....	.....	.....	.....	.....	..	..	..	.....

1.5 gm. per pound of body weight per day. A predigested protein preparation (Nutramigen, Protolysate, or Probana) is recommended because these foods provide easily absorbable amino acids. A variety of milk preparations modified by the removal of some fat and the addition of amino acid mixtures and one of the readily available carbohydrates may also be used. An additional consideration is that of the curd tension of the formula. By using the predigested protein formulas having a low curd tension, the stools are likely to be soft. Occasionally intestinal obstruction may result from the formation of hard casein curds within the intestine. Two patients developed this complication and required operative procedures to relieve the obstruction. Patient 20 in the present series was receiving an evaporated-milk formula and developed intestinal obstruction at 2 months of age. The other patient, successfully relieved of meconium ileus by surgery, was given a Nutramigen formula and was doing well. When changed to a whole-milk formula at the age of 4 months he developed signs of intestinal obstruction within a week. At operation fecal impactions were noted. He died at 6 months, in November, 1952, and is for this reason not included in this report. A similar ex-

TABLE 2.—*Intestinal Obstruction (Meconium Ileus) in Newborn Period—Nonoperative Cases*

Patient	Birth Date	Sex	Birth Weight, Lb.-Oz	Days in Hospital	Discharge Weight, Lb.-Oz.	Duodenal Intubation		Sweat Electrolytes, mEq./L.			Onset Pulmonary Symptoms	Current Chest Findings by X-Ray	Age Antibiotics Begun	Present Status (July, 1955)			
						Age	Results	Age, Yr.	Na	Cl				Antibiotics*	Pancreatin*	Nutritional (Weight Percentile)	Pulmonary
16	10/21/41	M	7-7½	10	5-12	2 days 3 10/12 yr.	Scant flow; 0.2 ml. in 3 hr. Neg. for trypsin	13 7/12	121.2	118.2	Approx. 1 mo.	Atelectasis, bronchiectasis	6 8/12 yr.	C	C	12	Moderate
17	1/7/48	M	8-1½	7†	6-3	Not done	.....	6 4/12	135.0	130.0	6 wk.	Increase in bronchovascular markings, mild	6 9/12 yr.	I	I	35	Mild
18	4/8/50	F	7-6½	25‡	....	2 wk. 4 yr.	Neg. for trypsin Viscid; amylase, lipase, trypsin absent	4 5/12	149.9	138.0	2 wk.	Irregular bronchovascular markings, patchy areas of irregular density	2 wk.	C	C	50	Mild
19§	1/10/52	F	5-2	35‖	5	3 1/12 yr.	Scant; viscid; amylase, lipase, trypsin absent	3 1/12	123.0	151.0	None	Normal	Not given	0	0	10	Normal
20	5/29/53	F	5-8	12	5-2	6 days	Scant fluid; amylase, lipase, trypsin absent	.....	.....	.....	2 mo.	Atelectasis right middle lobe; irregular areas of aeration and emphysema	2 mo.	C	I	10	Moderate lobectomy October, 1954

* C indicates continuous; I, intermittent.
† Born at Cambridge City Hospital; first seen by us at 5 10/12 years.
‡ Boston Floating Hospital.
§ This patient first seen by us at 3 1/12 yr. and diagnosis of cystic fibrosis made.
‖ Newberry, S. C.

perience was noted by Rosenblum.‡ Large fecal masses may form in the intestinal tract of patients with cystic fibrosis at any age and may cause relatively little discomfort. Efforts should be made to minimize the formation of fecal impaction in small infants who have undergone intestinal surgery, especially in a group of patients such as these, who are more prone to develop this complication.

Multivitamin preparations are suggested in amounts approximately two times the daily allowance recommended by National Research Council. Oily preparations of vitamins A and D are poorly absorbed by these infants and should be avoided. Since vitamin K absorption may be impaired and the formation of prothrombin depressed, added vitamin K is indicated, especially in the smaller infants. Sodium chloride in liberal quantities should be provided, especially in warm weather, when excessive loss through sweat may occur.

While an occasional infant may show satisfactory progress without pancreatic substitution therapy, the majority of patients require this therapy to improve their defective digestion. In small infants receiving formulas of protein hydrolysates, the administration of pancreatin is not necessary. However, when solid foods are added to the diet the administration of pancreatin is advised. The preparations we employ are Viokase (whole pancreas) § in powdered or tablet form or Panteric Granules ‖ (triple-strength pancreatin). An occasional patient is unable to tolerate these preparations. This was noted in Patient 3, who developed diarrhea whenever Panteric Granules or Viokase was given. In spite of his not having this therapy, his growth proceeded at a remarkably rapid rate. Pancreatic substitution therapy was provided continuously to 11 patients. We have arbitrarily regarded therapy, whether substitution or antibiotic, as "continuous" when it has been administered satisfactorily for over 80% of the time the patient has been under observation.

The majority of infants with meconium ileus develop pulmonary symptoms during the first few months of life, as noted in Tables 1 and 2. In three infants (Patients 6, 11, 19) symptoms referable to the respiratory tract were absent, and the most recent films of the chest were interpreted as normal. In the remaining patients pulmonary signs and symptoms appeared in spite of the early institution of antibiotic therapy.

Roentgenographic examination of the lungs revealed uniform changes varying only in degree of involvement. These changes consisted of irregular aeration, increased bronchovascular markings, lobular atelectasis, emphysema, and bronchiectasis. Two patients (Patients 7 and 20) had right-middle-lobe atelectasis. In Patient 20, the atelectasis was detected at 2 months of age and persisted for 15 months in spite of repeated attempts to relieve the obstruction by bronchoscopy. Inasmuch as the remaining lung appeared relatively uninvolved, a lobectomy was performed at 17 months of age. The postoperative course was smooth, and the child continues to do well. Her progress during the first year is shown in Chart 1. Roentgenograms of the chest taken on Sept. 28, 1954, and on June 2, 1955, are presented in Figures 1 and 2. The other patient with a right-middle-lobe atelectasis has extensive involvement of both lungs, and lobectomy is not deemed advisable.

The Staphylococcus is usually the predominant micro-organism in the nasopharynx of these infants and plays a significant role in the pulmonary infection. Prophylactic and therapeutic measures are aimed at preventing or alleviating obstructive phenomena due to mucous secretions and infection due to the Staphylococcus. These measures include the use of expectorants, bronchodilators, oxygen, humidity, and antibiotics. The use of streptokinase and streptodornase to remove obstructing plugs of mucus from the larger bronchi under bronchoscopic guidance has

‡ Rosenblum, H.: Personal communication to the authors.

§ Obtained from VioBin Corporation, Monticello, Ill.

‖ Parke, Davis & Company.

INTESTINAL OBSTRUCTION WITH MECONIUM PLUG
Relief without Operation

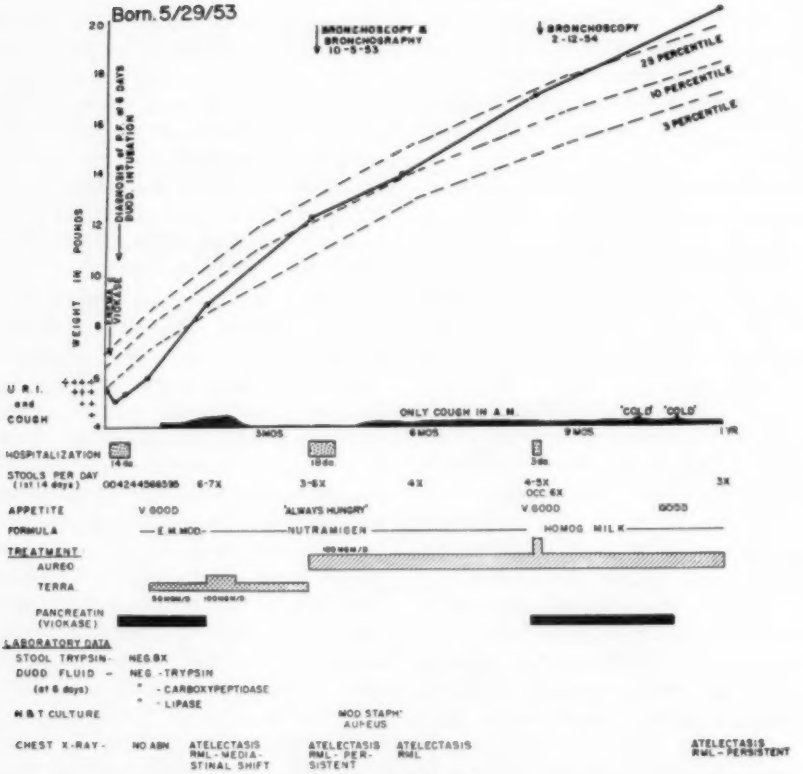


Chart 1.—Patient 20.

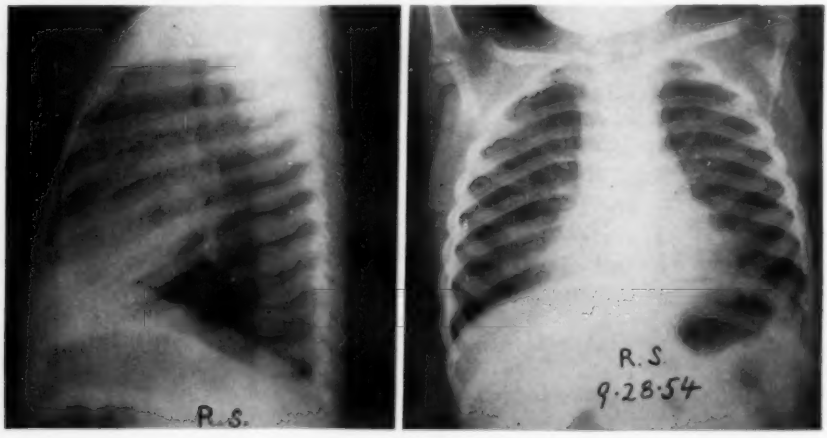


Fig. 1.—Patient 20

Fig. 2.—Patient 20.

not been successful. Postural activities to promote drainage have been used when practical. Broad-spectrum antibiotics are employed prophylactically, but once infection is established the presently available antibiotic and chemotherapeutic agents are used in therapeutic doses either singly or in combination. We have used chlortetracycline (Aureomycin), oxytetracycline (Terramycin), chloramphenicol, tetracycline, erythromycin, and sulfadiazine in an attempt to prevent or control the pulmonary infection. The usual dosage of the broad-spectrum antibiotics varied from 10 to 25 mg/kilogram/day in one or two divided doses. The use of penicillin and streptomycin by aerosol two or three times daily for short periods has proved very effective. The penicillin and streptomycin are mixed so that 1 ml., which is the amount usually nebulized, contains 500,000 units of penicillin and 50 mg. of streptomycin. A more detailed description of antibiotic therapy with chlortetracycline and oxytetracycline has been presented.¶

Antibiotic therapy was begun at the time of admission in the surgically treated patients in most instances, except in the first two patients, who were treated before broad-spectrum antibiotics were available. Once begun, the antibiotics were given continuously in all but four patients. By continuous therapy we refer to daily administration with not more than four weeks' omission during a year. By intermittent therapy we refer to the use of antibiotics irregularly, at intervals varying from a few weeks to several months. The patients who were given antibiotics intermittently had minimal pulmonary involvement and for the most part were given antibiotics only during acute respiratory infections. One patient (Patient 19), Table 2, had no antibiotics, and two others (Patients 16 and 17) were started on antibiotics at 6 8/12 and 6 9/12 years of age, respectively.

LABORATORY STUDIES

The duodenal fluid was examined in 17 of the 20 patients. In 11 infants this test was performed during the initial hospitalization. Characteristically the fluid was scanty and viscid, with no demonstrable activity for pancreatic lipase, amylase, and trypsin. It should be recalled that amylase is normally absent from the duodenal fluid in infants under 6 months of age. In six patients the duodenal assay was performed after the age of 6 months, and in each instance no amylase activity was found. In two patients, repeat duodenal enzyme assays were carried out 3 years 10 months and 4 years after the initial study, and again no pancreatic enzyme activity was detected. The methods employed have been described.[20]

The sweat sodium and chloride concentration was measured in 19 patients following a mild thermal stimulus by a method devised in our laboratory.# The concentration of sodium and chloride in the sweat was above the normal range in every case studied. For diagnostic purposes we consider the range 60 to 70 mEq/liter as the upper limit of normal for both sodium and chloride. The values found in these 17 patients are in the same range as those found in patients with an onset of their disease later in infancy. The mean values noted in healthy children and sick controls are 30.5 mEq/liter for

¶ References 21 and 22.

References 20 and 23.

Fig. 3.—Patient 11 on Feb. 28, 1955.

Fig. 4.—Patient 1. Left, July 20, 1950. Right, July 12, 1954.

sodium and 35.3 mEq/liter for chloride. The corresponding values in patients with cystic fibrosis are 119.0 mEq/liter for sodium and 129.8 mEq/liter for chloride.

PRESENT STATUS OF PATIENTS

In evaluating the condition of the 20 patients at the time of writing, the percentile weight * is recorded as a reflection of the nutritional status. It is noteworthy that nine patients are at or above the 35th percentile in weight. Four patients are below the third percentile.

The pulmonary involvement in each patient is gauged by the clinical and roentgenologic findings. In three patients (Patients 6, 11, 19) pulmonary symptoms are absent and x-rays of the chest are normal. These patients are now $5\frac{2}{12}$, $2\frac{7}{12}$, and $3\frac{6}{12}$ years old, respectively. Figure 3 shows Patient 11 in this group. For convenience of discussion the remaining 17 patients are classified into three groups in order of severity of pulmonary involvement: mild, moderate, and severe.

* The percentile charts were prepared by Dr. Harold Stuart, Harvard School of Public Health.

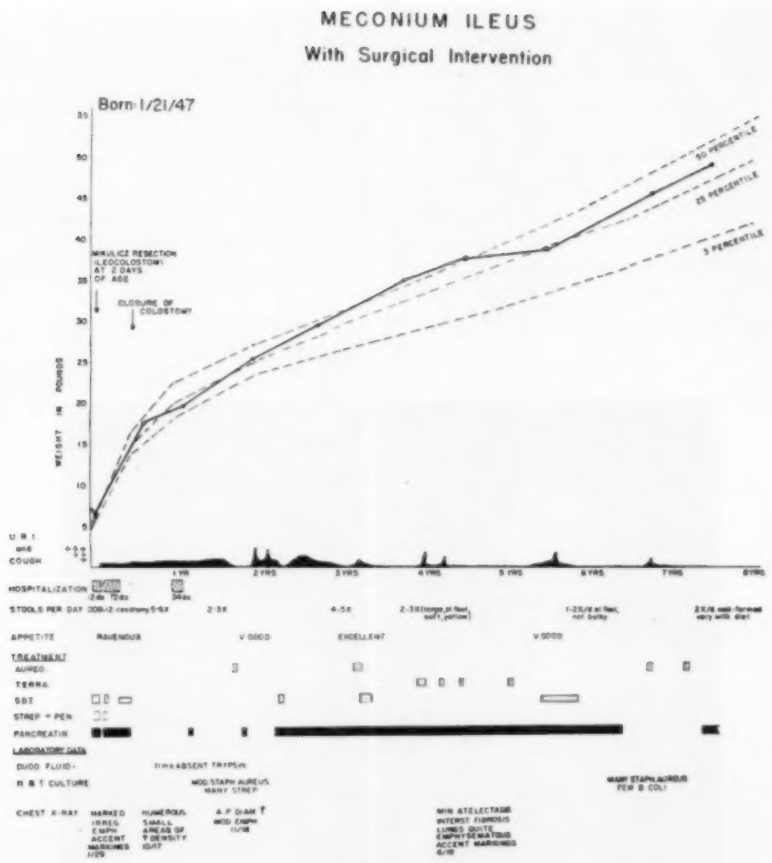


Chart 2.—Patient 1.

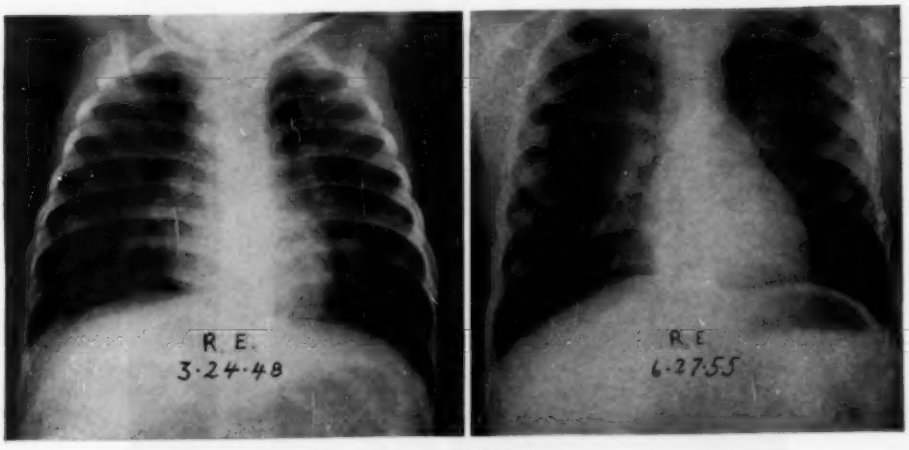
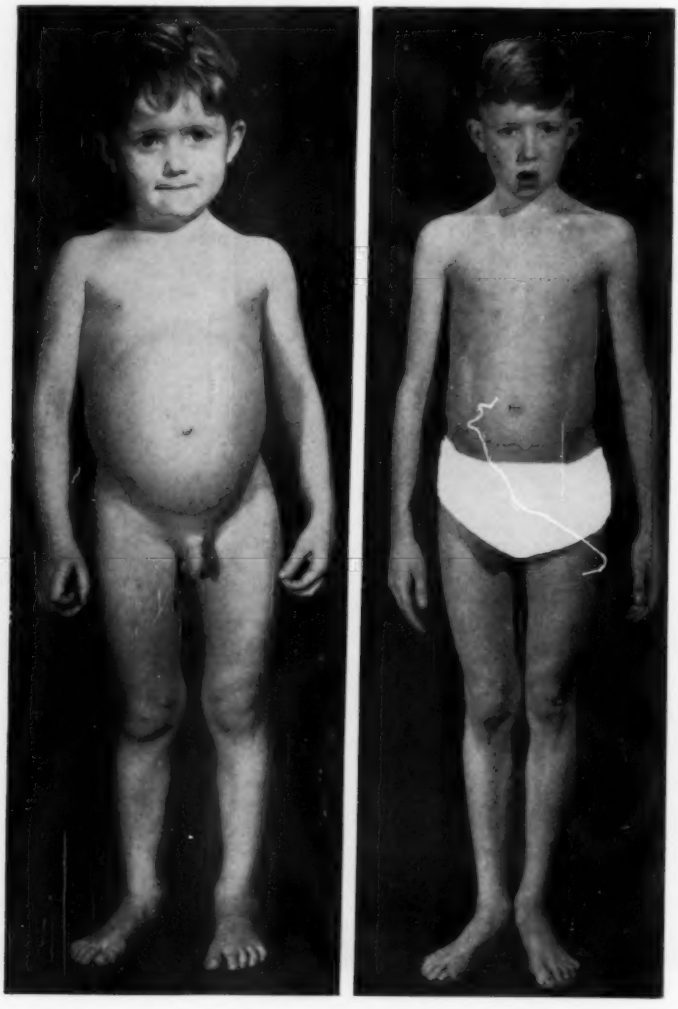


Fig. 5.—Patient 1.

In the group with mild pulmonary involvement we include those patients with an infrequent cough, without physical findings in the lungs, and with minimal emphysema and atelectasis by x-ray. The pulmonary reserve appears good as judged by normal physical activity. Six patients, ranging in age from 2 9/12 years to 8½ years, are in this mild group (Patients 1, 4, 5, 10, 17, 18). The oldest patient in this group, Patient 1, is shown in Figure 4. His clinical course is depicted in Chart 2. Figure 5 shows some of the roentgenograms taken in early infancy, March 24, 1948, and a recent chest film, June 27, 1955.

The patients with moderate pulmonary involvement have more frequent cough, especially after exercise. They are dyspneic on exertion. The physical examination usually reveals an increased anteroposterior diameter of the chest, with no constant auscultatory findings. One may note retraction of the intercostal muscles with inspiration, hyperresonance, wheezing respiration,

Fig. 6.—Patient 16. Left, March 3, 1946. Right, Feb. 11, 1954.



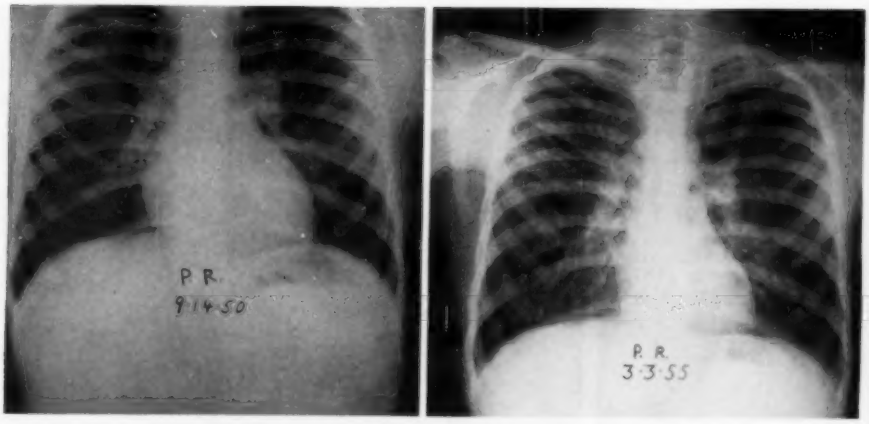


Fig. 7.—Patient 16.

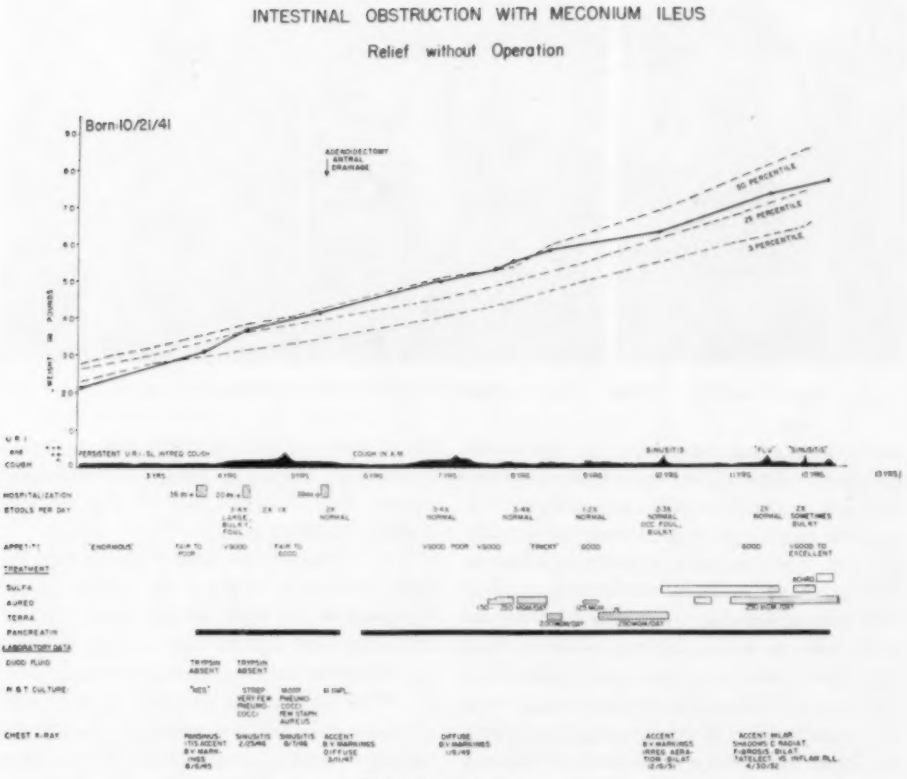


Chart 3.—Patient 16.

Fig. 8.—Patient 3 on Feb. 9, 1954. Fig. 9.—Patient 8. Left, Dec. 13, 1951. Right, July 15, 1954.

coarse rhonchi, and, rarely, rales. The roentgenogram of the chest depicts diffuse atelectasis and emphysema with increased bronchovascular markings. Digital clubbing may be present. For the most part, the children in this group are able to maintain normal or near-normal activities, i. e., attend school and play actively with children of their own age. There are seven patients (Patients 3, 12, 13, 14, 15, 16, 20), ranging in age from 6 months to 13 9/12 years, in this group with moderate pulmonary involvement. Figure 6 shows the oldest patient in this group. Chest films taken on Sept. 14, 1950, and on March 3, 1955, are shown in Figure 7. His clinical course is shown in Chart 3. Figure 8 is Patient 3 of this group.

The children with severe pulmonary involvement have frequent and severe coughing spells which often awaken them through the night and disturb sleep. These children are unable to maintain normal physical activity. They tire readily and are dyspneic with the least exertion. The physical examination usually reveals a malnourished, dyspneic child with an emphysematous chest. Pigeon

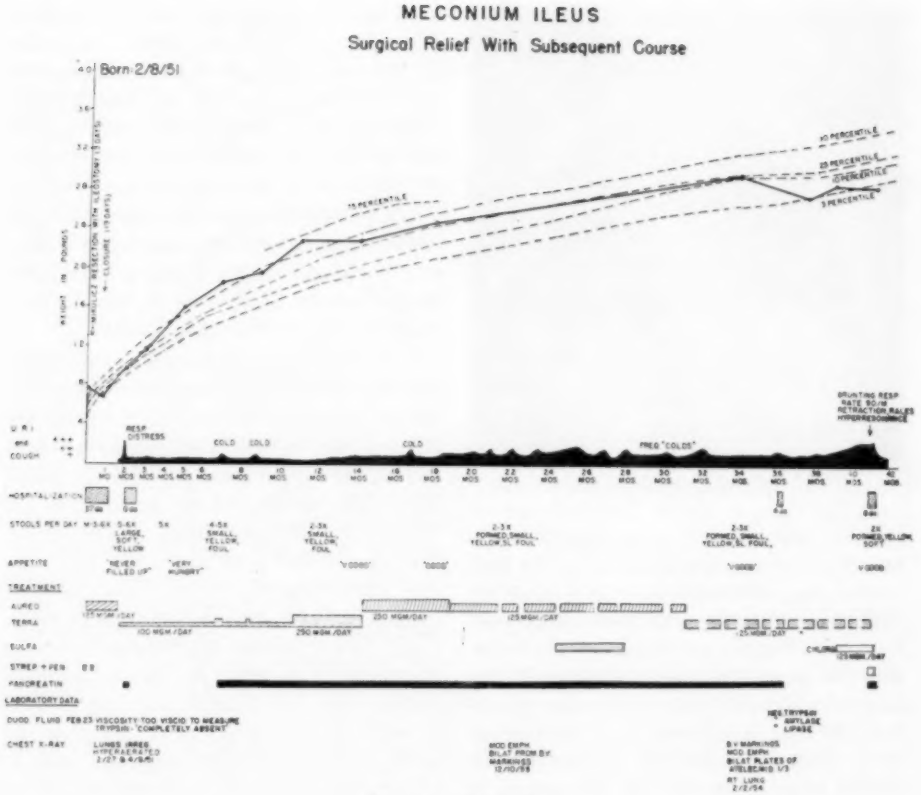


Chart 4.—Patient 7.

deformity of the chest is often noted. Intercostal retractions with deep inspiration may be detected. Rales are frequently heard and may persist over involved areas for long periods of time. The roentgenogram of the chest shows, in addition to the findings mentioned in the moderate group, more widespread areas of infection. Bronchiectasis is commonly suspected from the appearance of the films. Lobar atelectasis may be noted. Two patients (Patients 7 and 8) fall in this group. The clinical course of Patient 7 is depicted in Chart 4. Patient 8, now 3 9/12 years of age, represents the most advanced case in this series. A photograph and selected chest films are shown in Figures 9, 10, and 11.

Two patients (Patients 2 and 9) are difficult to classify and fall in between the moderate and severe groups. The present status of the patients does not appear to be directly related to the age of onset of pulmonary symptoms nor to the time initial antibiotic therapy was begun.

The prolonged and continuous use of chlortetracycline and oxytetracycline in a dosage of not more than 25 mg/kilogram/day did not produce any serious toxic or deleterious effect. In five patients the duration of therapy exceeded five years. In a few instances dark brown to black staining of the temporary teeth was noted. Moniliasis was not a problem in the patients reported on.

We were unable to detect clinical evidence of vitamin A or D deficiencies. In two patients (Patients 2 and 4) gastrointestinal bleeding occurred in early infancy and was thought to be due to vitamin K deficiency

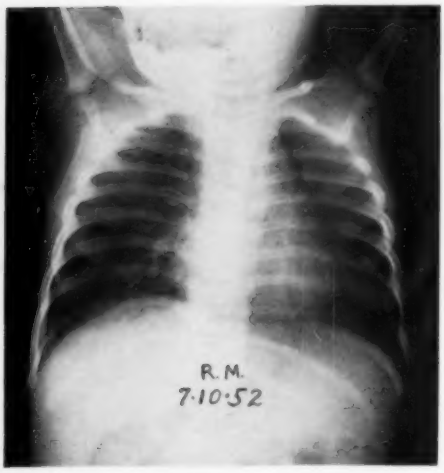


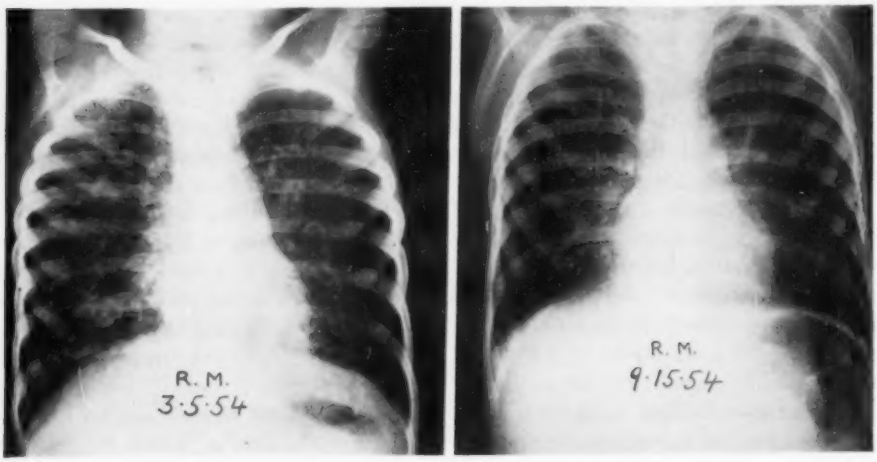
Fig. 10.—Patient 8.

because of the abnormal prothrombin time and the favorable therapeutic response with vitamin K. Subsequent patients were given vitamin K routinely, and this problem did not recur. We did not recognize riboflavin, thiamine, or nicotinic acid deficiency in our patients. Anemia, hypoproteinemia, or evidence of liver involvement was not encountered. Gastrointestinal series in two patients were interpreted as normal. However, in Patient 16, the gastrointestinal series taken at $3^{10}/_{12}$ years showed a grossly abnormal small-bowel pattern, with marked dilatation of many of the jejunal loops. The ileum showed a solid column of barium, with areas of dilatation and areas of hypertonicity. There was also a delay in the motility. This examination was made before therapy was initiated.

One patient (Patient 2) fractured her left radius and ulna following a fall from a pony at $3^{11}/_{12}$ years. Patient 7 fell and fractured his left clavicle at 3 years of age. In both cases healing progressed satisfactorily.

A brief statement concerning the family history will be made because of the hereditary nature of cystic fibrosis. In 5 of the 20 families the patient with meconium ileus was an only child. In 10 families in which the patient had one sibling, six siblings are living and well, one is living and has cystic fibrosis, one died after premature birth, and two died with meconium ileus. In four families where there are two siblings, seven are in good health and one has cystic fibrosis. In one family in which the patient had three siblings, two are healthy and one died as a result of meconium ileus. In these 20 families, meconium ileus occurred once in 17 families and twice in 3 families. Out of a total of 41 pregnancies in the 20 families, 23 resulted in infants with meconium ileus,

Fig. 11.—Patient 8.



2 in infants with cystic fibrosis, and 15 in apparently normal children.

The order of birth of the patient in the 10 families with two pregnancies was first in four cases and second in six cases; in 2 families meconium ileus occurred with each of two pregnancies, and in 4 families in which there were three pregnancies meconium ileus occurred first in two instances and third in the other two cases.

COMMENT

Our experience bears out Farber's prediction, made in 1943, that infants with meconium ileus who survive surgical correction would subsequently develop manifestations of cystic fibrosis. We have not encountered any exceptions to this statement, although, when made, it was of theoretical interest only, as there were no reported survivors among patients with meconium ileus. The surgical correction of this condition was considered hopeless until 1948, when Hiatt and Wilson [2] reported the survival of five of eight patients after surgical intervention. The ages of the survivors at the time of the report was as follows: 26, 26, 15, 3½, and 2 months.

For the 10-year period 1945 to 1955, a total of 61 patients with meconium ileus have been operated upon by the Surgical Service of the Children's Medical Center. Of these, 25 were successfully relieved of their obstruction. Eight of these patients subsequently died. In one patient there is a question concerning the diagnosis, and the other survivor has been seen by us too recently to be included in Table 1. This patient at the age of one year has no pulmonary symptoms, appears well, and is on constant antibiotic and replacement therapy.

Meconium ileus may be difficult to differentiate clinically from other forms of intestinal obstruction. At times the roentgenologic examination of the abdomen may reveal a mottled or granular appearance of the meconium seldom if ever seen in other forms of intestinal obstruction of the newborn.[24] In the patients recently studied at the Children's Hospital a preoperative diagnosis has been made in approximately 70% to 80% of cases.[3] In the presence of a positive family history of cystic fibrosis or of a previous child with meconium ileus the clinical impression may be strengthened. It has been our policy to inform the attending obstetrician of the possibility of the occurrence of meconium ileus in the offspring of pregnant mothers who had previously given birth to an infant with meconium ileus or cystic fibrosis.

The question arises as to whether it is possible to establish the diagnosis of meconium ileus with certainty prior to operation. Duodenal intubation is difficult and impractical in the majority of these infants. The measurement of sweat electrolytes following a thermal stress is also impractical at the age of 1 or 2 days. The assay of meconium for trypsin is not of diagnostic assistance because in our experience tryptic activity is usually reduced in normal meconium. Chemical studies of meconium may be employed to differentiate meconium from patients with meconium ileus from normal meconium (Patients 17, 18, 19). Observations made in our laboratory indicate that a simple test for the presence of protein is sufficient to make the distinction. A protein material is readily precipitated from an aqueous extract of meconium (upon the addition of 10% trichloroœcetic acid) from the patients with meconium ileus, whereas very little or no precipitate is formed from the extract of normal meconium. In spite of this useful chemical test the surgeon's task and responsibilities remain unaltered, inasmuch as the method of obtaining a sample of meconium would be by operative means in the majority of cases.

Previous observers have commented on the variation in the degree of intestinal obstruction caused by the abnormal meconium in these infants. This is clearly brought out in this report. In one group of patients the obstruction was so mild that relief was accomplished by nonsurgical means. The frequency of this mild form of obstruction is difficult to estimate. Although we report

on five patients, this represents a small number when viewed as part of the total number of patients with meconium ileus requiring surgery. Bodian [14] refers to three similar patients, and Swain and France [25] to one patient. An additional patient, now 8 years of age, was seen by one of us (H. S.) through the courtesy of Dr. Birch, of Youngstown, Ohio. It is of interest that the majority of patients seen later in infancy with signs and symptoms of cystic fibrosis fail to give a history of intestinal obstruction in the newborn period. It is very likely that a small number of cases of mild forms of intestinal obstruction due to meconium ileus escape unrecognized in the newborn nursery. To treat all patients with meconium ileus expectantly with the hope that the patient may "unplug" can lead to disaster.

In the patients treated surgically, varying lengths of intestinal segment were resected because of the varying degrees of obstruction encountered. Indeed, in six cases resection was not necessary. In some reports, the surgeon attempts to remove the meconium manually, with saline washes and enzyme solutions and by whatever means comes to mind. In a case report from the Children's Memorial Hospital [26] approximately 500 cc. of saline was injected into the bowel to free the meconium from the mucus membrane. From a transverse ileal incision near the ileocecal valve long pieces of ropey meconium were milked and pulled from the lumen. One piece of meconium was at least 3 feet long. Olim and Ciuti [27] have recently had two successful experiences with the use of a solution of 0.8% hydrogen peroxide. In one case, a cast of meconium appeared after it was loosened from the intestinal wall. The gravity of meconium peritonitis resulting from perforation is emphasized by Koop,[28] who stated in 1953 that before 1950 there were no reports of survival in meconium peritonitis, and even now survivals are not common. Two of our patients have survived this serious complication, Patient 1, who is now 8½ years of age, and Patient 4, who is 6 years of age.

We have not been impressed with the presence of associated anomalies or congenital defects, an association frequently noted by others.† There are times when the surgeon may mistake meconium ileus for an ileal atresia, especially when the hypertrophied and distended ileum is contrasted to the small, empty, and hypoplastic large intestine. Rare instances where both conditions coexist have been noted.

Not all infants with difficulty in expelling meconium during the first day or two of life have meconium ileus, nor will they subsequently develop evidence of pancreatic insufficiency. One of us (H. S.) has a vivid recollection of a one-day-old infant with signs of intestinal obstruction. The consultant applied firm and gentle pressure over the baby's distended abdomen, and a large meconium plug was expelled. This practice is not recommended! This patient was observed for a period of 3½ years, during which time he showed no evidence of pancreatic insufficiency. His duodenal fluid was examined when he was 3½ years of age and found normal for amylase, lipase, and trypsin activity. Difficulty in expelling meconium may be due to a variety of other conditions, including volvulus, congenital anomalies, intra-abdominal tumors, defects of a neurogenic nature, weak peristaltic movements as seen in debilitated infants and premature infants, and perhaps some unexplained reasons.

The medical management of patients with meconium ileus following recovery from surgery is essentially similar to that for patients with cystic fibrosis unassociated with ileus in the newborn period. However, the problems immediately following the initial operation may be manifold. The importance of the early introduction of broad-spectrum antibiotic therapy should be stressed. Other considerations involve the placing of the baby in a tent where oxygen and a mist or humid environment can be achieved. A saturated solution of potassium iodide given orally in a dosage of 1 to 3 drops (0.06 to

† References 10 and 29.

0.18 cc.) two to four times a day may help "thin" out the bronchial mucus. In addition, one must consider the use of pancreatic preparations or of normal duodenal fluid to irrigate the intestinal tract at frequent intervals through the ileostomy openings, and the proper use of intravenous fluids, including blood, plasma, dextrose, electrolytes, and multivitamins. Vitamin K should be given by the parenteral route during this initial postoperative period. This is of practical importance, as two of our earlier patients, who had not been given vitamin K, had gastrointestinal hemorrhage secondary to prothrombin deficiency. The ileostomy should be closed without delay.[3]

The merit of antibiotic and pancreatic replacement therapy is clear in most cases; when these agents are stopped we observe a deterioration in the patients' condition. However, in a few patients, parents see no beneficial effect of pancreatin. We do not have metabolic balance data to back up the claim of parents in these few instances. The frequency with which the pulmonary changes advance without therapy in most patients suggests that our efforts be directed to halt this progression. The infectious process may be dealt with and at times kept under control for prolonged periods. The mechanical problems due to the formation of thick mucus secretions may augment the effects of infection and present more formidable therapeutic problems. No satisfactory explanations have been presented to explain why some patients show rapid progression of their pulmonary lesion and others very little or none at all. This variation in the natural history of the disease complicates therapeutic evaluation. However, in a condition which formerly had been considered almost uniformly fatal, the recording of a large group of survivors suggests effective measures. When extensive structural damage occurs, we are apt to consider the lesion irreversible. That early pulmonary changes may be reversible is documented by the history of Patient 6. During his first two years roentgenograms of his chest showed patchy areas of emphysema, with areas of atelectasis and increased vascular markings. The film suggested the diagnosis of cystic fibrosis. Now, at age 4, the roentgenograms reveal a normal lung architecture.

One of the serious pulmonary features of cystic fibrosis in small infants is the occurrence of lobar atelectasis.[20] This finding was made in two patients (Patients 7 and 20). In one patient (Patient 20) a lobectomy was performed, and in the other the changes in the remainder of the lungs were too extensive to attempt removal of the collapsed lobe.

It was formerly believed that patients with meconium ileus represented the severest form of cystic fibrosis and accordingly had the poorest prognosis. This belief is no longer justified. With successful relief of the obstruction the prognosis depends upon the severity and rate of progression of the pulmonary manifestations rather than upon the intestinal and pancreatic dysfunction. The child with the stormiest course following surgery is now progressing satisfactorily without replacement therapy and receives antibiotic treatment only during respiratory infections (Patient 1). The course of this patient is to be contrasted with the course of another patient, not included in this report, whose meconium ileus was relieved spontaneously. She died at the age of 5 years with extreme pulmonary pathology. Her failure to thrive was adequately explained by the early collapse of the right upper lobe at 4 months of age and its persistence. During the last two years of her life she had remained below the 3d percentile for weight and between the 3d and 10th percentiles for height.

The laboratory investigations carried out in our patients included the duodenal intubation usually performed during the first month and the thermal sweat test whenever practicable; this latter test, based on the original observation of di Sant'Agnese and co-workers,[21] became available in July, 1954.[22] The results of the sweat test reveal the same elevated levels of sodium and chloride as detected in patients with a later onset of cystic fibrosis. These tests were

carried out during the past year, when the patients studied varied in age from 6 months to 13 7/12 years; so we are unable to state what the tests would have shown had they been done during the first few months of life. From our present fragmentary data it appears that repeat tests performed as far apart as one year show essentially the same findings. We should also point out that the level of sweat sodium and chloride concentration noted does not correlate with the age of the patient or with the severity of the intestinal, pancreatic, or pulmonary process and has no prognostic significance. Measurements of the electrical conductance of sweat were carried out in a number of patients and here too the values are significantly elevated, approximately three to four times greater than those of the control patients.[32]

The study of the duodenal fluid in all but one case was characteristic of complete pancreatic insufficiency. Trypsin was absent, as were lipase and chymotrypsin and carboxypeptidase, when these measurements were made. The fluid was scanty in amount and viscid. In one patient (Patient 14) the initial examination of the duodenal fluid at one month showed some lipolytic and tryptic activity. This finding was disturbing when first obtained and suggested that perhaps a laboratory error had been made. A repeat examination at 5 months of age revealed the absence of tryptic activity and a trace of lipase activity. Accepting the hypothesis that meconium ileus is due to the interaction of two factors, abnormal gastrointestinal secretory activity and pancreatic dysfunction, it may be possible to explain our finding. The viscid pancreatic fluid with some tryptic and lipolytic activity may represent the activity of a partially or spottily involved pancreas. Indeed, pathological examinations of microscopic sections from the pancreas of fatal cases of meconium ileus do not always show the same degree of involvement. This was pointed out by Denzer, Zuelzer, Andersen, Farber, Craig, and others.

The estimation of the over-all incidence of cystic fibrosis in any community based on the frequency of meconium ileus cannot be made with accuracy. There is no fixed ratio of meconium ileus patients to patients with a later onset of cystic fibrosis. The number of patients found to have cystic fibrosis will increase in proportion to the awareness of the physicians of this possibility and the availability of simple, reliable diagnostic procedures. Inasmuch as the majority of patients with meconium ileus are called to the attention of the surgeon or pathologist, the number of cases in any one region are apt to be recorded and may represent a fairly constant number. In our institution, the average number of cases per year for the past 10 years has been about six. The ratio of patients with meconium ileus to those with cystic fibrosis will decrease as the clinical cases of cystic fibrosis are more easily diagnosed. In 1947, we encountered approximately 7 patients with cystic fibrosis for 1 case of meconium ileus, whereas last year we found over 10 new patients with cystic fibrosis for every 1 case of meconium ileus. This ratio is further distorted when dealing with certain families where the incidence of recurring meconium ileus is high, as exemplified in one family in which four of five children died of meconium ileus.

SUMMARY

Our experience with the medical management of 20 patients with meconium ileus is described. Fifteen patients were successfully relieved of their obstruction by surgery and five by medical means. The age range of the patients in July, 1955, is 7 months to 13 9/12 years. A brief historical account is presented. Reference is made to a simple method of differentiating normal meconium from that derived from patients with meconium ileus.

The clinical course of the patients following relief of their obstruction is similar to the course of patients with cystic fibrosis (whose onset is later in infancy). The common belief that meconium ileus always means a poor prognosis and represents the severest form of cystic fibrosis is not upheld. The degree of intestinal obstruction bears no

direct relationship to the ultimate outcome. Following relief from the obstruction the prognosis depends upon the severity and rate of progression of the pulmonary lesion.

Charts, tables, and photographs illustrate various clinical and laboratory features of these 20 patients.

The present status of our 20 patients is summarized by stating that 5 are on or above the 50th percentile for their weight, 7 patients are between the 20th and 50th percentiles, 4 are between the 3d and 20th percentiles, and 4 are below the 3d percentile in weight. Inasmuch as the prognosis depends on the severity of the pulmonary lesion, an attempt is made to appraise this by clinical and roentgenologic study. Three patients appear to be free of pulmonary involvement, six patients show mild pulmonary involvement, seven moderate, and two severe. There are two patients that fall in between the moderate and severe groups. Patients may shift from one category to the next, and fortunately it is not always in the direction of increasing severity. Although this report is not overly optimistic, it helps to dispel the completely gloomy approach to the problem of meconium obstruction held by some surgeons at the present time.

300 Longwood Ave. (15).

REFERENCES

1. Lips, J. B., and Wiebenga, A. H.: Een Geval van pancreasfibrose bij een 18-jarige jongen, Nederl. tijdschr. geneesk. **3**:2500-2507, 1954.

2. Hiatt, R. B., and Wilson, P. E.: Celiac Syndrome: VII. Therapy of Meconium Ileus; Report of 8 Cases with Review of Literature, Surg. Gynec. & Obst. **87**:317, 1948.

3. Gross, R. E.: The Surgery of Infancy and Childhood: Its Principles and Techniques, Philadelphia, W. B. Saunders Company, 1953, Ch. 13.

4. Montgomery, W. F.: Meconium Ileus: Report of a Case with Successful Management, J. A. M. A. **152**:225, 1953.

5. Borenstine, J., and Printz, J. H.: Meconium Ileus (Complete Obstruction) in a Premature Infant, J. Pediat. **43**:209, 1953.

6. Landsteiner, K.: Darmverschluss durch eingedicktes Meconium: Pankreatitis, Zentralbl. allg. Path. **16**:903, 1905.

7. Dodd, K.: Intestinal Obstruction Due to Meconium Ileus in a Newborn Infant, J. Pediat. **9**:486, 1936.

8. Kornblith, B. A., and Otani, S.: Meconium Ileus with Congenital Stenosis of the Main Pancreatic Duct, Am. J. Path. **5**:249, 1929.

9. Hurwitt, E. S., and Arnheim, E. E.: Meconium Ileus Associated with Stenosis of the Pancreatic Ducts: A Clinical, Pathologic and Embryologic Study, Am. J. Dis. Child. **64**:443, 1942.

10. Andersen, D. H.: Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease: A Clinical Pathologic Study, Am. J. Dis. Child. **56**:344, 1938.

11. Farber, S.: The Relation of Pancreatic Achylia to Meconium Ileus, J. Pediat. **24**:387, 1944.

12. May, C. D., and Lowe, C. U.: Fibrosis of the Pancreas in Infants and Children: Illustrated Review of Certain Clinical Features with Special Emphasis on Pulmonary and Cardiac Aspects, J. Pediat. **34**:663, 1949.

13. Glanzmann, E.: Dysporia entero-bronchopancreatica congenita familiaris: Cystische Pankreasfibrose (Syndrom von Landsteiner-Fanconi-Andersen); Eine klinische Vorlesung, Ann. paediat. **166**:289-313, 1946.

14. Bodian, M., Editor: Fibrocystic Disease of the Pancreas: A Congenital Disorder of Mucus Production—Mucosis, New York, Grune & Stratton, Inc., 1953.

15. Denzer, B. S.: Meconium Ileus, Am. J. Dis. Child. **62**:1114, 1941.

16. Zuelzer, W. W., and Newton, W. A., Jr.: The Pathogenesis of Fibrocystic Disease of the Pancreas: Study of 36 Cases with Special Reference to Pulmonary Lesions, Pediatrics **4**:53, 1949.

17. Rapoport, S., and Buchanan, D. J.: Composition of Meconium: Isolation of Blood-Group-Specific Polysaccharides; Abnormal Composition of Meconium in Meconium Ileus, Science **112**:150, 1950.

18. Buchanan, D. J., and Rapoport, S.: Chemical Comparison of Normal Meconium and Meconium from a Patient with Meconium Ileus, Pediatrics **9**: 304, 1952.

19. Glanzmann, E., and Berger, H.: Über Mekoniumileus (Dysporia entero-broncho-pancreatica congenita): Klinische, pathologisch-anatomische Beobachtungen und chemische Untersuchungen des Darminhaltes bei einem am 6. Lebenstage wegen Mekoniumileus verstorbenen Neugeborenen, Ann. paediat. **175**:33, 1950.

20. Shwachman, H.; Leubner, H., and Catzel, P.: Mucoviscidosis, in Advances in Pediatrics, edited by S. Z. Levine, Chicago, Year Book Publishers, Inc., 1955, Vol. 7.

21. Shwachman, H.; Crocker, A. C.; Foley, G. E., and Patterson, P. R.: Aureomycin Therapy in the Pulmonary Involvement of Pancreatic Fibrosis (Mucoviscidosis), New England J. Med. **241**:185, 1949.

22. Shwachman, H.; Silverman, B. K.; Patterson, P. R., and Zheutlin, L. J.: Antibiotics in Treatment of Pancreatic Fibrosis, with Emphasis on Terramycin, J. A. M. A. **149**:1101, 1952.

23. Shwachman, H.; Dooley, R. R.; Higgins, E., and Stern, M.: Sweat Electrolytes in Cystic Fibrosis of the Pancreas, to be published.

24. Neuhauser, E. B. D.: The Roentgen Diagnosis of Fetal Meconium Peritonitis, Am. J. Roentgenol. **51**:421, 1944.

25. Swain, V. A. J., and France, N. E.: Intestinal Obstruction in the Newborn: Review of 32 Consecutive Cases, Lancet **1**:844, 1954.

26. Case Reports of The Children's Memorial Hospital, Chicago, Vol. 11, p. 3269, 1953.

27. Olim, C. B., and Ciuti, A.: Meconium Ileus: A New Method of Relieving Obstruction, Ann. Surg. **140**:736, 1954.

28. Koop, C. E.: Intestinal Obstruction in the Neonatal Period, in Advances in Pediatrics, edited by S. Z. Levine, Chicago, Year Book Publishers, Inc., 1953, Vol. 6, p. 63.

29. Rogers, J. D.; Baggenstoss, A. H.; Musgrove, J. E., and Kennedy, R. L. J.: Intestinal Obstruction Associated with Fibrocystic Disease of the Pancreas: Report of 3 Cases, Minnesota Med. **34**: 1075, 1951.

30. di Sant'Agnese, P. A.: Bronchial Obstruction with Lobar Atelectasis and Emphysema in Cystic Fibrosis of the Pancreas, Pediatrics **12**:178, 1953.

31. di Sant'Agnese, P. A.; Darling, R. C.; Perera, G. A., and Shea, E.: Abnormal Electrolyte Composition of Sweat in Cystic Fibrosis of the Pancreas: Its Clinical Significance and Relationship to the Disease, Pediatrics **12**:549, 1953.

32. Stern, M.; Licht, T., and Shwachman, H.: Electrical Conductivity of Sweat in Cystic Fibrosis, to be published.

News and Comment

ANNOUNCEMENTS

Clinic of Child Development.—The Department of Pediatrics of The Ohio State University and The Children's Hospital of Columbus, Ohio, announces the establishment of a Clinic of Child Development, which will concern itself with deviations from normal behavioral development in the preschool period from birth through 5 years. In addition to diagnostic evaluation, guidance in the management of problems and help in securing the necessary medical and community services will be provided.

Fellowships for a period of one year, with a stipend of $5000, are available beginning July 1, 1956, with one position each six months provided. Pediatricians who are trained will have opportunities to engage in research projects designed to elucidate the etiologies of the neuropsychiatric disabilities of childhood and to enter into the teaching program.

Address inquiries to Dr. Earl H. Baxter, Chairman of the Department of Pediatrics, The Ohio State University, or to Dr. Hilda Knobloch, Associate Professor of Pediatrics and Director of the Clinic.

Extramedullary Erythropoiesis in the Livers of Premature Infants

RODNEY S. FOWLER, M.D., Toronto, Canada

INTRODUCTION

In routine microscopic examination of tissue from premature infants post mortem, great variation in the amount of extramedullary hematopoiesis is observed.

In infants of a given birth weight the number of sites of extramedullary hematopoiesis and the amount in each organ varies greatly. An attempt has been made to evaluate some of the factors affecting extramedullary hematopoiesis.

METHODS

Since the widest variations seemed to occur in infants with birth weights between 500 and 2000 gm., this group was selected for study. In order to minimize changes in hematopoiesis due to age or postnatal disease, only those premature infants who died within 72 hours of birth were included. Within these limits of birth weight and age at death, consecutive cases were studied. Over a period of three years and two months, from January, 1950, to March, 1954, postmortem examination was made of 327 premature infants. Of this number, 205 fulfilled the requirements for the study, but the slides from five infants were not available. Consequently, all of the observations were made on the remaining 200 cases.

In this group there was a relatively high proportion of small premature infants because of their high mortality rate and because large numbers of these smaller infants are referred to this hospital by the Premature Transportation Service of the New York City Department of Health. The distribution of cases by birth weight is shown in Table 1. One hundred two infants had birth weights between 500 and 999 gm., and the remaining ninety-eight had birth weights from 1000 to 1999 gm.

TABLE 1.—*Distribution of Cases by Birth Weight*

Birth Weight, Gm.	No. of Cases
500- 599	14
600- 699	15
700- 799	22
800- 899	28
900- 999	23
1,000-1,099	15
1,100-1,199	13
1,200-1,299	20
1,300-1,399	10
1,400-1,499	12
1,500-1,599	9
1,600-1,699	8
1,700-1,799	5
1,800-1,899	4
1,900-1,999	2
	200

In order to assess the amount of hematopoiesis in the liver of each infant, a standard microscope was fitted with an eyepiece grid which measured 0.0256 sq. mm. under high power (× 430). The number of normoblasts and normocytes contained within the grid was counted in three widely separated areas of liver. Portal tracts and central veins were excluded from the field so that only liver parenchyma appeared within the limits of the grid. By this method, both fixed cells and those free in the sinusoids were counted. The total number of normoblasts and normocytes counted in three fields was recorded for each case. It was assumed that this figure was an indication of the amount of erythropoiesis present. Of the various erythropoietic cells, normoblasts and normocytes were chosen because of the ease with which they could be differentiated from other cells in the liver.

The measurement was easily made in most cases. However, in those livers in which the erythropoietic cells were concentrated in focal areas, the selection of representative fields was more difficult. An attempt was made to select for counting a field representative of three different areas of liver. Another difficulty was encountered when some of the erythropoietic cells were degenerating and their

Submitted for publication Sept. 17, 1955.

Clinical Fellow in Pediatric Pathology.

From the Department of Pathology, Columbia University College of Physicians and Surgeons, and Babies Hospital, New York.

TABLE 2.—*Distribution of Cases by Amount of Erythropoiesis*

Total No. of Normoblasts and Normocytes in 3 Fields in Liver *	No. of Cases
0- 49	1
50- 99	7
100-149	12
150-199	28
200-249	29
250-299	32
300-349	32
350-399	16
400-449	17
450-499	13
500-549	4
550-599	6
600-649	1
650-699	1
700-749	1
	200

* Mean, 364 ± 123.

nuclei had become fragmented. The total number of original cells was estimated by observing the relation of fragments to one another and by noting the limits of cytoplasm where it remained.

All of the slides were examined without knowledge of the clinical history. The results obtained in this way were then analyzed, and an attempt was made to correlate clinical and pathological data with the amount of erythropoiesis.

RESULTS

Table 2 shows the distribution of cases according to the number of normoblasts and normocytes counted in three fields in the liver. The total count varied from 38 to 731, with 91 cases having counts over 299 and the remaining 109 cases having counts below. One mother of the group was a known diabetic. Her infant weighed 1300 gm. at birth, and the count was 412. There was only one known case of erythroblastosis fetalis, in an infant who had a birth weight of 875 gm. and a count of 296. Both of these infants died on the second day.

(a) Relation of Birth Weight to Erythropoiesis

The cases studied were divided into three birth-weight groups, and the mean value for erythropoiesis with its standard deviation in each group was calculated. For the 500-999 gm. group, the mean was 327 ± 136; for the 1000-1499 gm. group, 285 ± 121, and for the 1500-1999 gm. group, 225 ± 79. As noted in Table 3, the difference between the mean value of Group 2 (1000-1499) and that of Group 3 (1500-1999) is greater than would reasonably be expected to occur through chance variation alone ($P < 0.01$). A difference as great as that noted between the mean value of Group 1 (500-999) and Group 2 (1000-1499) is unlikely to be due to chance variation but is of borderline significance ($P < 0.05$). Within limits, the amount of hepatic erythropoiesis tends to vary inversely with the birth weight.

This relationship was examined in another way (Table 4) using the "fourfold" table (with Yates' correction *). The association between birth weight (<1000 gm. versus> 1000 gm.) and degree of erythropoiesis (count <300 versus count >300) was found to be a significant one ($P < 0.01$).

(b) Relation of Age to Erythropoiesis

In normal full-term infants, extramedullary hematopoiesis disappears after 5 days of age.† In the present series of premature infants, 87 died in the first 24 hours, 89 died between 24 and 48 hours, and 24 died between 48 and 72 hours. Approximately two-thirds of those infants that died in the first 24 hours had erythropoiesis values over 300, while only 3 of 25 infants dying between 48 and 72 hours had values over 300 (Ta-

* References 3 and 4.

† References 1 and 2.

TABLE 3.—*Average Erythropoiesis in Three Weight Groups*

Weight, Gm.	No. of Cases	Mean and Standard Deviation	Difference of Means	Standard Error of Difference	Difference / S. E. Diff.
500- 999	102	327 ± 136	42	19.8	2.1
1,000-1,499	70	285 ± 121	60	20.8	2.9
1,500-1,999	28	225 ± 79			

TABLE 4.—*Relation of Birth Weight to Erythropoiesis* *

Birth Weight, Gm.	Cell Count	
	< 300	> 300
< 1,000	46	56
> 1,000	63	35

* $\chi^2 = 6.682$; $P < 0.01$.

TABLE 5.—*Relation of Erythropoiesis to the Age at Death* *

No. of Cases

Erythropoiesis	Day of Death		
	I	II	III
< 300	30	58	21
> 300	57	21	3

* Comparison of Day I with Days II and III: $\chi^2 = 23.5$; $P = < 0.001$.

TABLE 6.—*Relation of Birth Weight to the Age at Death* *

Birth Weight, Gm.	Day of Death		
	I	II	III
< 1,000	47	45	10
> 1,000	40	44	14

* Comparison of Day I with Days II and III: $\chi^2 = 0.59$; $P = 0.50$.

TABLE 7.—*Relation of Erythropoiesis to Hyaline-Membrane Disease* *

	Erythropoiesis	
	< 300	> 300
Hyaline membrane	45	39
Without hyaline membrane	64	52

* $\chi^2 = 0.033$; $P = > 0.80$.

TABLE 8.—*Relation of Vaginal Bleeding to Birth Weight* *

	Birth Weights, Gm.	
	< 900	> 900
Vaginal bleeding	19	14
No vaginal bleeding	60	107

* $\chi^2 = 4.54$; $P = < 0.05$.

TABLE 9.—*Relation of Erythropoiesis to Vaginal Bleeding in the 500-1,000 Gm. Group* *

	Erythropoiesis	
	< 475	> 475
Vaginal bleeding	16	8
No vaginal bleeding	70	8

* $\chi^2 = 5.75$; $P = < 0.02$.

ble 5). Grouping infants dying in the second and third 24-hour periods together to make the calculation simpler, χ^2 is 23.5 and P is less than 0.001. This highly significant relationship supports the view that the amount of erythropoiesis decreases rapidly in the first three days of life.

The relation of birth weight to the day of death was investigated to be sure that this factor was not playing a part in the above result. It can be seen from Table 6 that an approximately equal proportion of infants who died on each of the first three days after birth weighed more and less than 1000 gm. at birth. When the χ^2 test is applied to these data, it emphasizes that there is no relation between birth weight and time of death during the first three days.

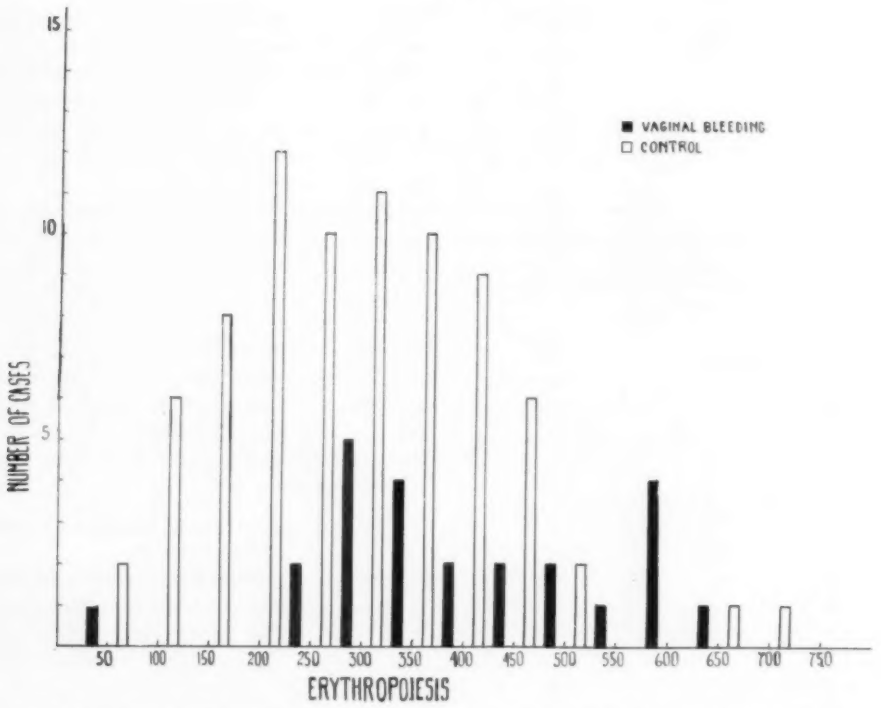
(c) Relation of "Hyaline-Membrane Disease" to Erythropoiesis

Jordan states that the formation of erythropoietic cells depends on the CO_2 concentration in the cell environment.[5] It is also probable that the amount of extramedullary erythropoiesis is affected by anoxia. One of the common causes of anoxia in the premature infant during the first few days of life is "hyaline-membrane disease."

In the present study no significant difference was found in the amount of erythropoiesis in cases with and without "hyaline-membrane disease" (Table 7).

(d) Relation of Vaginal Bleeding in the Mother to Extramedullary Erythropoiesis

The instances in which there was a maternal history of vaginal bleeding during pregnancy, excluding those with bleeding just before delivery due to placenta previa, were compared to those without such a history. There were 33 born of mothers with known vaginal bleeding and 167 controls. Since a difference in the birth-weight distribution of these two groups would affect any comparison between them, they were examined for such a difference using the χ^2-test (Table 8). Over half of the cases in the vaginal-bleeding group had birth weights under 900 gm., in contrast to almost two-thirds of the cases in the control group, who had birth



Comparison of erythropoiesis in the livers of premature infants with a birth weight of 500-1000 gm., with and without a history of maternal vaginal bleeding.

weights over 900 gm. Since premature infants born of mothers with a history of vaginal bleeding have lower birth weights than do controls, only infants under 1000 gm. were used for comparison of the degree of erythropoiesis. The Chart shows a frequency distribution of the cell counts in the cases in this weight group. There were 24 cases with birth weights of 500 to 1000 gm. and a history of vaginal bleeding and 78 controls. It can be seen that the curve for the vaginal-bleeding group is bimodal. The group of cases with excessive erythropoiesis is interesting. By the χ^2-test the cases with a history of vaginal bleeding are found to have a statistically significant excess of hematopoiesis (Table 9) (χ^2=5.75 and P=between 0.02 and 0.01). There were insufficient numbers in the remaining weight groups to draw any valid conclusions.

In the 24 cases with vaginal bleeding in the history and with birth weights from 500 to 1000 gm. there were 10 deaths in the first 24 hours, 12 deaths in the second 24 hours and 2 deaths in the third 24 hours. In the 78 cases without vaginal bleeding, there were 37 deaths in the first 24 hours, 33 deaths from 24 to 48 hours and 8 deaths from 48 to 72 hours (Table 10). There was no significant difference between the age at death of infants of mothers with and without vaginal bleeding.

TABLE 10.—*Relation of Vaginal Bleeding History to Age at Death in Cases with Birth Weights Between 500 and 1,000 Gm.**

	Day of Death	
	I	II & III
Vaginal bleeding	10	14
No vaginal bleeding	37	41

* $\chi^2 = 0.06$; $P = < 0.90$.

In order to be sure that within the 500 to 1000 gm. weight group there is no significant difference in weight between the cases with

and without a maternal history of vaginal bleeding, the birth-weight distribution in the two groups was compared, using the χ^2-test. In the vaginal-bleeding group there were 14 cases with birth weights over 750 gm. and 10 cases with birth weights under 750 gm. In the control group there were 46 cases with birth weights over 750 gm. and 32 cases with birth weights under 750 gm. The proportions of each group over and under 750 gm. are approximately equal, and χ^2 is 0.03. With this value, $P>0.80$, indicating no significant difference. Therefore, the excessive erythropoiesis in the livers of premature infants with birth weights between 500 and 1000 gm. and with a maternal history of vaginal bleeding is unlikely to be due to low birth weight or to early death alone, but to some additional factor.

COMMENT

The significance of the results relating to vaginal bleeding is of greatest interest in this study. The bleeding was probably due to many causes, but in some cases, at least, it was due to some abnormality of the placenta. Possibly this abnormality was of such a nature as to interfere with the oxygenation of fetal blood. Since a group of premature infants born to mothers with this history have significantly more erythropoiesis in the liver than do their controls, it is conceivable that their excess erythropoiesis is due to chronic anoxia in utero. Besides, since the birth weights of these premature infants are significantly lower than those of control premature infants, it is possible that the premature onset of labor was due to the placental anomaly or to chronic fetal anoxia. It is reasonable to suspect that the amount of erythropoiesis depends to some extent on the oxygen tension of the blood, because islands of erythropoiesis are often found in the livers of older infants dying of cyanotic congenital heart disease. Also, the maximal amount of erythropoiesis in the liver is found in severe anemias of infancy and childhood—the classic example being erythroblastosis fetalis. The explanation for the large amount of erythropoiesis in many cases in our study which did not have a maternal history of vaginal bleeding might well be chronic intrauterine anoxia, and the cause of premature birth in these cases might have been an abnormality of the placenta or the fetal anoxia itself.

SUMMARY AND CONCLUSIONS

A method of assessing the amount of erythropoiesis in the liver is described. With this technique, 200 premature infants with birth weights between 500 and 2000 gm. who died within 72 hours of birth were studied. The following conclusions were reached:

1. Within wide limits the amount of erythropoiesis in the liver tends to vary inversely with the birth weight.

2. The amount of erythropoiesis decreases with increasing age during the first three days of life.

3. The presence of "hyaline-membrane disease" has no effect on the amount of erythropoiesis in the first three days.

4. Premature infants born of mothers with a history of vaginal bleeding during pregnancy have lower birth weights than do their controls.

5. The amount of erythropoiesis in the livers of premature infants in the birth-weight group 500-1000 gm. born to mothers with a history of vaginal bleeding during pregnancy is greater than in the control group, regardless of weight or day of death. The possibility that this may result from chronic intrauterine anoxia is discussed.

Dr. Dorothy H. Andersen assisted in the preparation of this paper.

REFERENCES

1. Gilmour, J. R.: Normal Hæmatopoiesis in Intra-Uterine and Neonatal Life, J. Path. & Bact. **52**:25, 1941.

2. Potter, E. L.: Pathology of the Fetus and the Newborn, Chicago, Year Book Publishers, Inc., 1952, p. 537.

3. Fisher, R. A.: Statistical Methods for Research Workers, Ed. 6, Edinburgh, Oliver & Boyd, 1936.

4. Hill, A. B.: Principles of Medical Statistics, Ed. 5, London, Oxford University Press, 1951, p. 140.

5. Jordan, H. E.: Extramedullary Hematopoiesis, Physiol. Rev. **22**:375, 1942.

Studies in Rheumatic Fever

1. Nutrition as a Factor Conditioning the Incidence and Course of Rheumatic Fever
2. Experience Since the Advent of Corticotropin and Cortisone
3. Effect of Activity and Rest on Nutritional State in Rheumatic Fever

JOSEPH A. JOHNSTON, M.D., Detroit

1. NUTRITION AS A FACTOR CONDITIONING THE INCIDENCE AND COURSE OF RHEUMATIC FEVER

A voluminous literature stresses the predilection of rheumatic fever for the children of the lower economic strata. "No disease has a clearer-cut social incidence than acute rheumatism which falls perhaps thirty times as frequently upon the poorer children of the industrial town as upon the children of the well-to-do. I agree with those who hold that the incidence increases directly with poverty, malnutrition, over-crowding and bad housing." [1] In Marshall's [2] series of 180 cases only 8 cases of rheumatism and carditis and 1 of chorea and carditis occurred in his upper economic group. Warner's [3] study showed a low intake of milk in the affected group. "Perhaps the most striking fact suggesting that an increase in animal fat in the form of fresh milk and butter may be of prophylactic value is furnished by the figures from Christ's Hospital where the incidence of rheumatism was reduced to less than a third corresponding to a rise in the animal fat consumption from 50.6 to 103.6 gm., due largely to an increase in the rations of milk and butter." Of equal importance, of course, could be the coincident increase in intake of protein and calcium contributed by milk. Peete [4] felt that the same factors conditioning rickets were important as a conditioning background for rheumatic fever—deficiencies in protein, calcium, phosphorus, and Vitamin D. Coburn and Moore [5] concluded that "deficiencies in several factors may be more important than a deficiency in any one dietary factor in conditioning the subject to the rheumatic state." Their observation of the frequency with which eggs were absent from the diets of rheumatic children and the reduction in the incidence of recurrences following streptococcic infection when eggs were added to diets otherwise adequate except for vitamin D and possibly ascorbic acid is interesting in the light of a similar finding by Wallis.[6] He speculates that a possible explanation for their usefulness may be in supplying a good source of choline: "The inhibitor of hemolytic activity of Streptolysin S-9 produced by group A streptococcus depends in part on serum phospholipid, one of whose ingredients is choline, a substance which can neither be synthesized nor stored in significant amounts." In 14 rheumatic children from wealthy homes, Coburn and Moore noted an absence of eggs in the diet in 10, of whom 4 were thought sensitive to them and 6 simply refused them. The objection frequently brought forward that the prevalence of rheumatic fever in Army

Received for publication Aug. 27, 1955.

Supported in part by a grant from the Michigan Heart Association.

From the Department of Pediatrics, The Henry Ford Hospital, Pediatrician-in-Chief, and the Edsel B. Ford Institute for Medical Research.

The laboratory determinations for the balance studies were under the supervision of Dr. O. H. Gaebler, of the Institute of Medical Research, and were performed by Lois Beers, B.S., and Rosemary Holland, B.S. Mrs. Wertz supervised the diets, and Miss Edna Jahraus, the calculations. Miss Ann Johnston and Miss Winnie Weber helped in tabulating the data. Dr. A. Ashley Weech subjected some of the material to statistical analysis.

and Navy recruits excludes nutrition as a serious conditioning factor is gratuitous. The nutritional state of the young man of 20 may reflect deficits acquired 15 years previously, which may not be made up by an adequate diet for months or even years. Even when an adequate diet is offered, as I have previously shown in tuberculous adolescents whose dietary habits had been established over the years in poor homes, a preference for carbohydrate and an actual aversion from protein may have developed, so that in a self-selection study an analysis of refused food brings out a striking difference between the diet offered and the one consumed. Only one-third of the subjects selected an adequate intake of protein.[7]

There are presented here (1) an analysis of the outcome of rheumatic fever in children followed for varying periods up to 26 years correlated with the nutritional state, as judged by the Wetzel grid, when the illness manifested itself; (2) a correlation of the dietary history, as related to the intake of egg, meat, milk, and a source of vitamin D, with the outcome, and (3) balance studies for nitrogen and calcium for such inferences as might be drawn from them on the previous state of the stores of these items.

Correlation of Outcome with Wetzel Grid Rating

The Wetzel grid approach to classifying the nutritional state of children with rheumatic fever has been made previously. Kahn and co-workers[8] state that "growth failure is apparently almost a constant finding in children with rheumatic fever," and Higgons and associates[9] point out that the deflection to the right on the grid may precede the symptoms and findings which make the diagnosis definite. To the extent that the grid rating may be accepted as reflecting "nutrition," the majority of our children were of average or above average nutrition. It is our impression that children from any nutritional stratum may acquire the disease—the factors of infection, allergy, and inheritance would surely cut across all strata—but that the difference in outcome may be conditioned by the nutritional state.

The outcome in 230 cases seen between 1928 and 1949, and their standings on the Wetzel grid when first seen, are plotted in Figure 1 and Table 1. While a division was made between those seen before and after 1938, it could not be shown that there was a statistically significant difference in outcome between the two groups, and in the

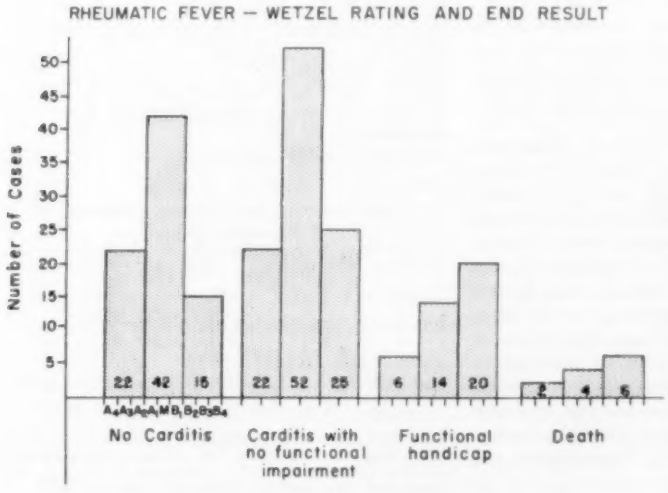


Fig. 1.—Frequency of Wetzel grid ratings correlated with outcome. Skewing to the left results from including more than an average number of "good" and "stocky" persons; skewing to the right, from a disproportionate number of "fair," "borderline," and "poor," cases.

TABLE 1.—*Wetzel Rating and Outcome in Rheumatic Fever*

	Wetzel Rating*	Patients, No.			
		No Carditis	Carditis with no Functional Handicap	Carditis with Functional Handicap	Death
1928-1938	A1, A3, A2	8	14	6	0
	A1, M, B1	14	27	5	3
	B2, B3, B4	6	13	12	3
1938-1949	A4, A3, A2	13	10	1	0
	A1, M, B1	26	25	9	3
	B2, B3, B4	8	13	6	4

* For purposes of constructing a contingency table, we considered channels B2, B3, and B4 as "below average" and channels A2, A3, and A4 as "above average." The outcome of the process is classified in Table 2.

TABLE 2.—*Contingency Table for 230 Cases*

	Cases, No.		
	Satisfactory Outcome*	Unsatisfactory Outcome*	Total
Nutrition average or above	138	26	164
Nutrition below average	40	26	66
Total	178	52	230

* Satisfactory, no carditis or carditis with no functional handicap; unsatisfactory, carditis with functional handicap or death.

The value of χ-square computed from this table is 14.9, which corresponds to a probability integral (P) of 0.0001134; that is, the probability that such a result could have resulted from chance alone is of the order of 1 in 10,000.

contingency table they are grouped together (Table 2). A murmur of any grade found in association with other evidence of rheumatic fever was accepted as evidence of carditis. For the statistical treatment of the data, I am indebted to Dr. Ashley Weech, whose further comments on this item follow:

Preliminary statistical tests fail to demonstrate any difference between the effects of "average nutrition" and "above average nutrition." Indeed, the effects of these two classifications of nutritional status are so similar as to suggest identity. Accordingly, for the purposes of our analysis the two groups can be combined. Likewise, I fail to find reliable evidence that an "unsatisfactory outcome" is better defined by "death" than by "functional handicap." It may be guessed that the failure results from the small number of total deaths but, whatever the reason, the result means that statistical analysis will gain in sensitivity by treating the two groups together (as defined by "unsatisfactory outcome").

CORRELATION OF OUTCOME WITH DIETARY HISTORY

With histories taken by a large number of different persons, the data can be considered to offer little more than a rough trend. The history form used calls for specific questioning on the intake of egg, meat, milk, and vitamin D. The analysis gives a suggestive but not highly significant result (Table 3).

In drawing inferences on nutrition from the dietary intake, it is important to remember that, particularly in the group for whom an adequate diet is available and even taken, factors interfering with its utilization may play the prominent role. In a study of 100 children, whom I considered poorly nourished, who had come from good homes, the diet offered seemed to play a role in less than 5%; in the others the highest percentage presented some condition interfering with the utilization of food, and high on the list was the infected tonsil. This is to hold no brief for tonsillectomy as a specific help in the rheumatic state. I would agree with Wilson[10]: "It is probable that the value of tonsillectomy in rheumatic children is proportionate to its influence on the general health of the child." We have previously shown the catabolic effect of infected tonsils as judged by the inability to store normal amounts of nitrogen and calcium with an adequate intake and the correction of this by tonsillectomy.* This type of nutritional defect is obviously not obtained from a dietary history but can be inferred from a careful history and physical examination.

* References 11 and 12.

TABLE 3.—*Dietary History and Outcome in Rheumatic Fever*

	Cases, No.		
	Outcome Satisfactory	Outcome Unsatisfactory	Total
Adequate diet	131	17	148
Inadequate diet	52	14	66
Total	183	31	214

The value of χ-square is 3.48, corresponding to a significance at about the level of confidence of 7%; i. e., the result could have occurred by chance 7 times in 100.

Inferences of Nutritional State from Balance Studies

There are no simple blood determinations which measure even fairly severe degrees of nitrogen and calcium deficiencies. Since both items, however, have "physiological ceilings," certain inferences on the state of the nitrogen pool and the calcium stores are possible from measurements of the degree of retention when the intake is adequate. Unusually high storage of these two items will be noted for as long as six months in a child whose previous intake of these has been low, following which, with intake unchanged, retentions will revert to the level expected for the age of the child. A second characteristic of the physiological process of replacing depleted nitrogen and calcium stores is the retention of large quantities of these items while weight is being lost or held level, a process of reconstituting tissue with the replacement of fat and water by nitrogenous tissue.†

Balance studies have been done on about 30 children with rheumatic fever, most of them during treatment with cortisone or corticotropin (ACTH). The metabolic changes during this treatment have been previously described.[14] Large losses of nitrogen occur during the first 10 days of treatment, and there is a marked drop in the metabolic rate; while in adults calcium is said to be affected in the same direction, in the children studied the pattern was not consistent, both anabolic and catabolic effects being noted. It is my feeling that one of the strongest influences on calcium retention is the state of the stores and that when these are low the catabolic effect of the hormone may be more than offset by the opposing tendency to replete stores. Another consistent effect has been the marked increase in appetite, so that urinary losses of nitrogen may quickly be offset by marked increases in intake; one child who would take no more than 5 gm. at the beginning of treatment was taking 17 gm. within 10 days. On withdrawal of hormone, or reduction in amount below a certain critical level, there is a rapid rebound of storage, with equilibrium being established in about two weeks. The first case presented describes the metabolic changes during the administration and gradual withdrawal of cortisone. Recovery from the initial large losses of nitrogen would seem to be complete between two and three weeks after the antianabolic effect disappeared, on reduction of dose from 300 mg. to 150 mg. of cortisone. In this case the high normal storage of calcium even while nitrogen was being lost probably reflects a previous deficit, the replenishment of which takes precedence of over any tendency to losses incidental to the use of cortisone.

† References 7 and 13.

Case 1.—A 14-year-old boy, born Aug. 4, 1937, was admitted on Aug. 5, 1951, with a history of joint pains of two months' duration, thought to be complicated by a heart involvement. On admission, which was because of an exacerbation of joint pains, the only evidence of carditis was a Grade 2 systolic murmur. P-R time was 0.17 second; Q-T time, 0.36 second; erythrocyte sedimentation rate, 40 mm. in an hour.

He was one of a family of nine children, and his mother stated that eggs, meat, and milk were offered except when cost was prohibitive and that eggs had been too expensive for a long time.

He was treated with cortisone, 300 mg. daily, from Oct. 5 to Oct. 20; 225 mg. daily through Oct. 24; 150 mg. through Oct. 31, and 50 mg. on Nov. 1 and Nov. 2. In addition, he received 1000 mg. of ascorbic acid on Oct. 5-7 and 200 mg. daily on Oct. 8 and thereafter. He received daily a teaspoon of a proprietary vitamin preparation (Multicebrin). Joint symptoms disappeared by Oct. 11; ESR fell from 40 mm. in an hour on Oct. 8 to 12 mm. in an hour on Oct. 25 (Fig. 2).

In the metabolic studies the changes were as follows (Table 4): Basal calories fell from 1657 to 1370 Cal. per 24 hours in 20 days, rising again slowly to 1492 Cal., the first rise occurring on the discontinuation of cortisone. A rise in intake of nitrogen from 18 gm. a day to 21.9 gm. a day was not sufficient to offset large increases in urinary losses, and for 15 days there was a large negative balance. Urinary nitrogen fell when the dose was reduced from 300 mg. to 225 mg. daily. The calcium balance was strongly positive (481 mg. a day) during the administration of cortisone but increased to 848 mg. a day on withdrawal. This is referable in part to a slight fall in both urinary and fecal calcium but in larger part to the increase in intake.

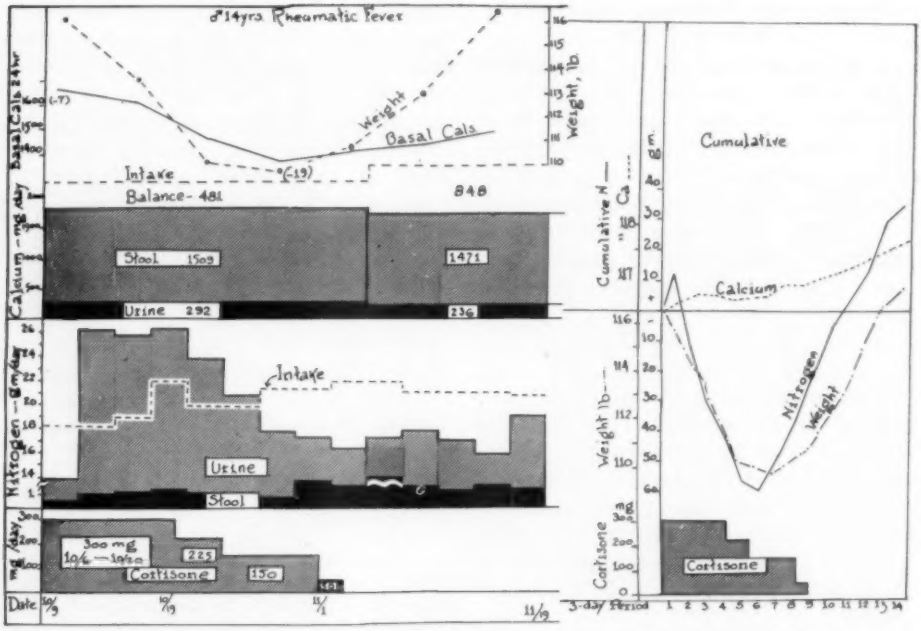


Fig. 2 (Case 1).—Metabolism during administration and withdrawal of cortisone. The anti-anabolic effect is no longer noted when the dose is reduced from 225 mg. to 150 mg. a day. Recovery to the precortisone level is effected in about 18 days. With the increased intake following cortisone, the net change in body composition in 42 days is reflected in the addition to body stores of 34.5 gm. of nitrogen and 23.24 gm. of calcium. Storage of this mineral is so high as to suggest previous deficits.

From the cumulative chart, it will be noted that the losses of nitrogen were made up and that there was a net gain of 24.5 gm. of nitrogen over the 42-day period. The large gain of calcium, both during the administration and following the withdrawal of cortisone suggests a previous state of depletion of this mineral.

Followed for three and one-half years, the patient shows no carditis and is playing competitive football.

Case 2.—A boy born June 25, 1936, and studied from June 17 to Sept. 19, 1951, at the age of 15, was the child of a broken home and a ward of the Juvenile Court. He had developed painful swollen

Table 4 (Case 1).—*Balance Observation Oct. 9 to Nov. 19, 1951*

6-Day Period No.*	Nitrogen, Gm./Day					Calcium, Gm./Day					B. M. R.†		Basal Cal.	Kg.	Diet Cal.
	Av. Urine	Av. Stool	Intake	Balance	Accumulation	Av. Urine	Av. Stool	Intake	Balance	Accumulation	B.	W.			
1	13.38	0.59	18.18	+4.21	+12.63	0.075	1.172	1.956	+0.709	2,127	−7	+9	1,658	52.843	2,600
2	25.14	1.05	18.18	−8.01	−11.40	0.300	0.842	1.956	+0.814	.....	...	...	.....	.....	.....
3	24.45	1.26	18.96	−6.75	−20.25	0.376	1.587	2.164	+0.201	.....	−9	...	1,603	51.482	3,000
4	24.72	1.48	21.90	−4.30	−12.90	0.474	1.641	2.520	−0.405	.....	...	...	.....	.....	.....
5	22.76	1.09	19.80	−4.05	−56.70	0.383	2.083	2.490	+0.024	4.029	−15	−2	1,454	50.008	.....
6	19.61	1.07	19.80	−0.88	−59.34	0.423	1.544	2.490	+0.523	.....	...	...	.....	.....	.....
7	16.93	0.78	21.30	+3.59	−48.57	0.275	0.802	2.250	+1.173	.....	−19	−8	1,370	49.781	.....
8	15.16	2.13	21.30	+4.01	−36.54	0.143	2.327	2.250	−0.220	.....	...	...	.....	.....	.....
9	14.54	1.78	21.90	+5.58	−19.80	0.184	1.584	2.460	+0.692	.....	−17	−5	1,418	50.235	.....
10	12.99	4.29	21.90	+4.62	−5.94	0.225	1.432	2.460	+0.803	12.942	...	...	.....	.....	.....
11	16.02	1.60	21.00	+3.38	+4.20	0.239	1.564	2.610	+0.807	.....	−16	−5	1,444	51.256	.....
12	15.57	1.42	21.00	+3.01	+13.23	0.249	1.359	2.610	+1.002	.....	...	...	.....	.....	.....
13	13.70	1.96	21.00	+5.34	+29.25	0.204	1.560	2.550	+0.786	.....	−15	−1	1,492	52.843	.....
14	17.42	1.59	20.76	+1.75	+34.50	0.263	1.444	2.545	+0.838	23.241	...	...	.....	.....	.....

* Cortisone was given during the first eight periods.
† B, basal metabolic rate calculated from the Boothby standards; W, from the Wetzel prediction.

joints two weeks after a throat infection. He gave a history of rheumatic fever which first occurred at the age of 10. He showed signs of aortic insufficiency with relative mitral insufficiency. B.P., 130/30. No history available of past diet. Nutritional state appeared poor (height 69¼ in.; weight, 124 lb., B3 classification on Wetzel grid). Teeth were so badly carious and infected as to necessitate later the removal of 10. The tonsils were frankly infected. Before admission here, he had received a week of 200 mg. of cortisone daily with no change in sedimentation rate, which on admission was 39 mm. in an hour.

Treatment consisted of 400 mg. of cortisone from June 13 to June 22 and 300 mg. from June 22 to July 8; ascorbic acid, 200 mg. daily; potassium acetate, 1 gm. daily. Diethylstilbestrol (Stilbestrol), 0.1 mg., was given every other day from July 10 to July 23. A second course of cortisone was given from July 23 to Sept. 7, starting with 300 mg. daily and steadily dropping to 25 mg. by decrements of 25 mg. Corticotropin, 20 mg. daily, was given from Sept. 4 to Sept. 8. Clinical improvement was rapid, but a recrudescence followed withdrawal of cortisone and a second course was given (Table 5).

Comment on Balance Study (Fig. 3).—The usual negative nitrogen balances followed the giving of cortisone, for 24 days in the first course and 18 days in the second. The rebound on withdrawal was of much larger magnitude than usual and may have been contributed to by the use of diethylstilbestrol. This was given because of severe acne (which incidentally improved during its administration) as well as to note its effect on the balances. In a previous study on adolescent girls,[15] I had shown that this preparation was catabolic for nitrogen and calcium.

On the other hand, in a study of the metabolic effects of testosterone administered to boys,[16] an anabolic effect was noted on nitrogen while the retention of calcium was consistently reduced. It is probable that this catabolic effect was being neutralized by the estrogens. In another case presented (H. J.) the estrogen was given simultaneously with cortisone and the anabolic effect on calcium was noted while nitrogen losses were continuing.

An outstanding finding was the magnitude of the storage of calcium. For 95 days the

TABLE 5 (Case 2).—*Balance Observation July 5 to Sept. 19, 1951*

Date	Nitrogen, Gm./Day				Calcium, Gm./Day										Treatment
	Av. Urine	Av. Stool	Intake	Balance	Accum. Urine	Av. Stool	Av. Urine	Intake	Balance	Accumulation	B. M. R.	Basal Cal.	Kg.	Ht., In.	Diet Cal.	
7/5-7/7	20.58	1.01	19.67	—1.92	—40.32	0.189	1.196	2.287	+0.902	18.942	—13	1,651	56.358	69½	2,800	Cortisone
7/8-7/10	21.39	0.60	20.70	—1.29	—44.19	0.182	0.917	2.670	+1.571	20.513	....	.....	55.108	....	3,000	Ratrogen
7/20-7/22	15.18	1.16	22.65	+6.26	+30.60	0.288	1.043	2.479	1.147	.....	....	1,846	.....	....	.....	Cortisone
8/7-8/9	23.90	1.06	20.84	—4.74	—54.69	0.210	1.614	2.353	+0.599	.....	....	1,778	.....	....	.. ..	.....
8/25-8/27	16.48	1.46	20.47	+2.53	—9.09	0.502	1.315	2.868	+0.866	.....	....	1,581	60.214	....	...	.....
9/18-9/19	11.92	1.10	20.55	+5.89	+112.79	0.198	0.791	2.161	+0.680	82.764	....	1,700	68.275	....	.....	.....

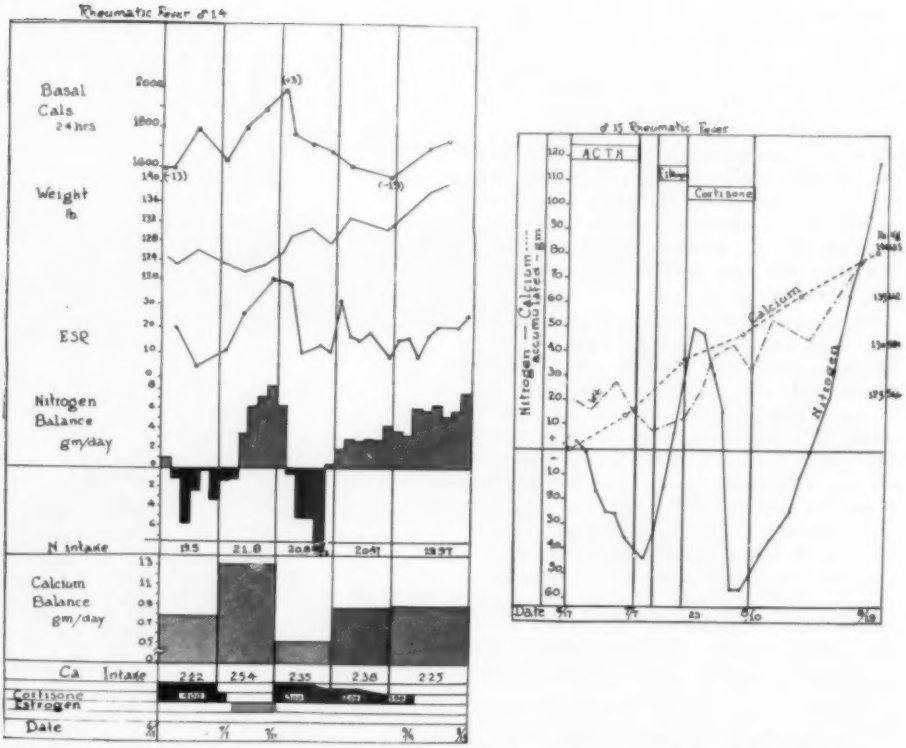


Fig. 3 (Case 2).—A 15-year-old boy, with poor nutritional background, chronic infection of tonsils and teeth, and a five-year history of rheumatic fever, showed the unusually large storages of calcium and nitrogen that reflect previous deficits. Estrogen was followed by anabolic effects on both items, though the nitrogen effect was probably largely due to the rebound phenomenon seen on withdrawal of cortisone, since only the calcium effect was noted in Case 3, when estrogen was given concurrently with the cortisone.

patient had an average retention of 871 mg. of calcium daily and of 1.18 gm. of nitrogen. The intake, governed by appetite, was inordinately high. It is my interpretation of this finding that storages as great as this (twice normal) carry with them the inference of a previous deficit. Comparably large retentions of nitrogen (5.95 gm. to 7.53 gm. daily) are noted in the last six three-day periods and carry with them a similar implication, though here interpretation is confused by the rebound phenomenon which regularly follows the withdrawal of cortisone.

Further Course.—This boy returned three years later and died in failure. His course was typical of that of a youngster neglected from childhood until at adolescence he was completely rebellious about cooperating with any program provided by foster-home agencies.

Case 3.—A Negro boy, born July 27, 1937, had a metabolism study from Oct. 6, 1953, to Dec. 22, 1953. He had been considered well until three months before admission, although a heart murmur was said to have been mentioned in school examination some years before. There were complaints of listlessness, anorexia, weight loss, and vague discomfort in the feet but no joint pains. His mother had rheumatic fever. One month before admission he was hospitalized elsewhere, was considered to be in cardiac failure, and was treated with cortisone, corticotropin, digitalis, and mercury diuretics. On transfer to this hospital, he had cardiac enlargement with prominence of the left auricular area, tachycardia, and a systolic murmur over the precordium, soft and intensified near the sternum. ECG showed a sinus tachycardia, right bundle branch block, and a definite abnormality in Lead V_6. ESR was 32 mm. in an hour.

Treatment was as follows:

	Date
Cortisone, Mg.	
150	9/22- 9/30
200	9/30-10/ 8
225	10/ 8-11/17
150	11/18-11/19
100	11/19-11/21
75	11/21-11/24
Diethylstilbestrol, 0.1 mg. every other day for seven doses	10/20-11/ 2
Ammonium Chloride, Gm.	
3	10/ 9-10/11
1.5	10/11-10/17
Theragran,* 1 capsule daily	10/ 9-11/24

* Theragran (Squibb) is a proprietary multivitamin preparation.

Metabolic Findings (Table 6 and Fig. 4).—The balances for both nitrogen and calcium were negative until the introduction of diethylstilbestrol, when the calcium balance became positive while the nitrogen balance continued negative. The large urinary losses are probably understood as referable to the ammonium chloride.

CASE 4.—A 10-year-old Italian girl developed acute tonsillitis one month before admission; for three weeks she had had fatigue and anorexia; for three days, swelling of the left wrist. There was a family history of rheumatic fever in a cousin. The dietary history told of aversion to meat, an intake of two or three eggs a week, adequate milk. Wt., 57 lb.; ht., 52½ in. (B2 Wetzel); temperature, 99.6 F; pulse rate, 112; respiration rate, 20; B.P., 115/70. She appeared pale. The left wrist was swollen and hot. The anterior cervical nodes were enlarged. There was a Grade 2 systolic murmur all over the precordium. The ESR was 40 mm. in an hour, and the antistreptolysin titer was more than 1000 Todd units. She received cortisone, 300 mg/day, from March 18 to March 29, when it was gradually reduced and replaced by corticotropin on March 31 and April 1. Salicylates were used on April 5 and May 6. Balance studies were done from June 3 through June 28, 1954, while she was still at bed rest except for bathroom privileges (Fig. 5 and Table 7).

The balance data show a high retention of nitrogen with a flat weight curve. This is longer following cortisone than would be explained as the recovery from that hormone and suggests the phenomenon of replenishing a deficit. Calcium storage was moderately low, as might be expected with rest.

2. EXPERIENCE SINCE THE ADVENT OF CORTICOTROPIN AND CORTISONE

Our early experience with cortisone and corticotropin was so impressive that we felt too prejudiced to withhold the hormones or to alternate cases and felt that we might make an assessment based on a comparison of the past 5 years with the previous 10. The strong evidence of a declining severity in this condition noted by Wallace and Rich [17] (and attributed in part to a general improvement in the level of nutrition) invalidates this approach to a large extent. Furthermore, influenced by two other studies,‡ we have in a third of the cases combined salicylates and ascorbic acid with the hormones, and so there are at least three variables. With these qualifications, and

‡ References 18 and 19.

TABLE 6 (Case 3).—*Balance Studies*

Date	Nitrogen, Gm./Day				Calcium, Gm./Day				Basal Cal. 24 Hr.	Treatment
	Urine	Stool	Intake	Balance	Urine	Stool	Intake	Balance		
10/6-20	17.84	1.51	13.20	−6.15	0.246	1.715	1.663	−0.298	1,449	Cortisone + NH_4 Cl, Theragran*
10/21-11/1	19.39	1.25	12.87	−7.77	0.289	1.011	1.280	+0.274	1,694	Estrogen
11/2-12/1	17.06	1.96	15.13	−3.90	0.280	1.550	1.766	−0.044	1,330	.....
12/8-12/22	14.02	1.90	18.24	+2.32	0.316	1.769	1.812	+0.043	1,776	Exercise

* A propietary multivitamin preparation.

TABLE 7 (Case 4).—*Balance Study Fifty-Five Days After Cortisone* *

No. of Days	Nitrogen, Gm./Day					Calcium, Gm./Day				
	Urine	Stool	Intake	Balance	Accum.	Urine	Stool	Intake	Balance	Accum.
24	5.13	2.08	11.38	+4.17	100.08	0.083	1.439	1.622	+0.155	3.72

Wt. at beginning, 33.5 kg. Wt. at end, 32.9 kg.
Mean basal Cal. per 24 hr., 1,135 (−3 Boothby, +1 Wetzel)

* The patient was ambulatory 30 minutes twice daily.

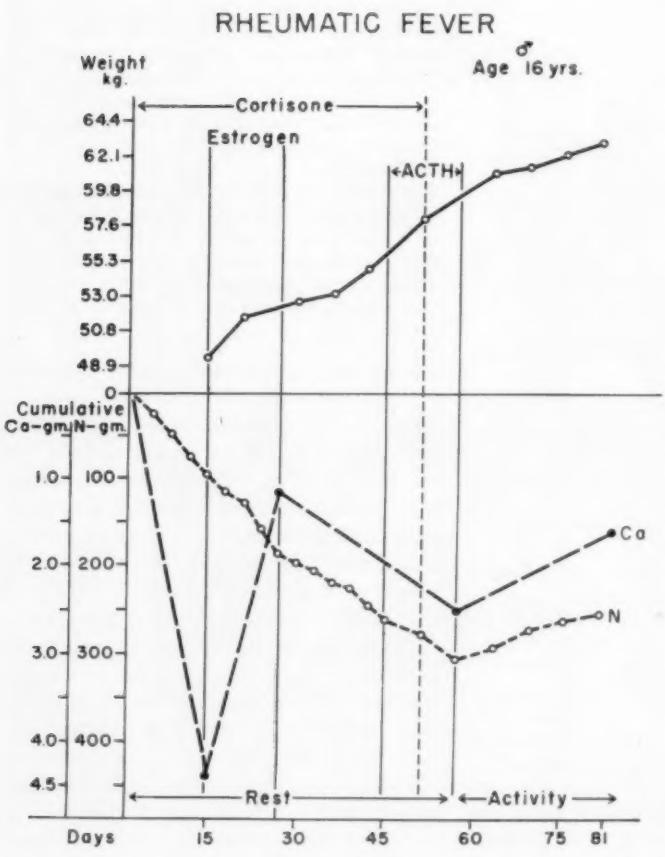


Fig. 4 (Case 3).—A boy, aged 16 years, had been at bed rest and under treatment for a month with corticotropin before this observation was begun. The catabolic effect on calcium was offset with diethylstilbestrol, given in this case concurrently with the cortisone. The introduction of moderate activity after 60 days was followed by a shift from negative to positive balances for both nitrogen and calcium.

bearing in mind the relatively negative results of the international study [20] with a one year follow-up, the results in the hormone-treated patients are presented in Table 8. Follow-up averaged 22 months, with 21 cases between 2 and 3 years, 5 between 3 and 4 years, and 4 between 5 and 6 years. The single death occurring in a child with his first attack was a fulminating case ending in death 12 hours after admission and after amounts of hormone were administered that we would now consider woefully inadequate. Two deaths occurred in boys who had had repeated attacks and fully developed valvular lesions when first seen.

TABLE 8.—*Cortisone- and Corticotropin-Treated Cases*

	Cases, No.	
	First Attacks	Recurrences
No carditis	38	5
Carditis with no functional handicap	11	15
Carditis with functional handicap	1	3
Death	1	2

A contingency table comparing outcome of these 76 cases, recurrences grouped with first attacks, with 270 cases seen before 1949 and using "satisfactory" and "unsatisfactory" in the same connotation as in the first Table gives for a value for χ-square of 9.58, corresponding to a probability integral (P) of 0.001970, a highly significant difference; the odds that the result could have occurred by chance are about 1 in 500.

It should be emphasized again, however, that we are apparently dealing with a milder disease and that we are describing the results of a regimen that combines salicylates, ascorbic acid, and hormones.

Bearing on the thesis of this study, however, that the end-result in rheumatic fever is conditioned by the nutritional state, we feel that one of the contributions of corticotropin and cortisone is the improvement in this state resulting from an increase in appetite and intake. Initial losses of nitrogen were usually quickly offset by increases in intake, so that in the cumulative balances large additions to the nitrogen pool are evident. When these have occurred in children previously malnourished, the nitrogen gains are not accompanied by corresponding gains in weight. The expected calcium losses did not occur in previously malnourished children. But even when excretion increased, it was commonly offset by increased intakes.

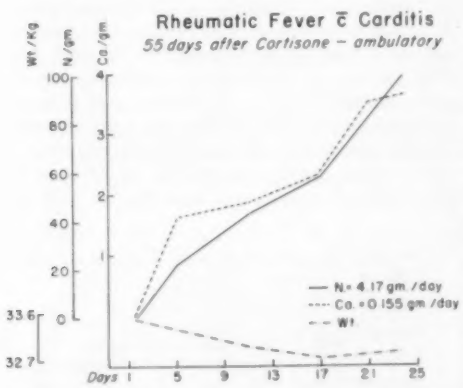


Fig. 5 (Case 4).—A girl, aged 10 years. Large gains of nitrogen with falling weight reflect previous deficits.

In two boys estrogen seemed to offset the catabolic effect on calcium. The possibility of neutralizing some of the adverse effects of the hormone needs further exploration. It has already been demonstrated that when it is used over long periods the "corticoid hypothyroidism" must be treated with thyroid if the cortisone is to be effective. In the relatively short periods during which cortisone is used in rheumatic fever, the fall in metabolism is probably one of its desirable effects.

3. EFFECT OF ACTIVITY AND REST ON NUTRITIONAL STATE IN RHEUMATIC FEVER

In a previous study [20] on the metabolic effects of bed rest, the literature is reviewed and the effects reported of rest and activity in patients with tuberculosis. If we accept the failure to retain normal amounts of nitrogen and calcium as one of the better indices of malnutrition in the growth period, and that the nutritional state plays a role in conditioning the outcome in rheumatic fever, then a consideration of anything which affects these items—the dietary intake, focal infection, hormones, inactivity—becomes pertinent to this thesis.

While the ill effects of bed rest seem more and more appreciated in chronic illness, there still seems to be hesitancy in applying the lesson to a condition involving the heart, and yet any advantage to be gained by reducing the work load must be weighed against the steady loss to the body of nitrogenous tissue. The amounts of activity necessary to offset disuse atrophy are small and can be obtained by slow walking about the ward or by simple pushing against a footboard, as we do in the case of the poliomyelitis patient. It will be shown that so long as the exercise does not result in significantly increasing pulse pressure and pulse rate its effect will be beneficially anabolic; pushed beyond that point it becomes catabolic.

In the study of the metabolic effects of cortisone there is included a long balance study (Case 3) [14] showing a constantly negative calcium balance for 72 days which promptly became positive when the patient was permitted to pedal the single-wheel mounted on the end of the bed for one minute twice a day. In two cases recorded in the present communication (Cases 3 and 4), the variable of activity was assessed. There are added here other studies, three of which (Cases 5, 6, and 8) have a bearing on this point.

CASE 5.—The patient, born Oct. 21, 1939, and studied from May 14, 1951, to July 6, 1951, was

a well-nourished boy of 11½ years, with a past history of comparative freedom from infection, who developed joint pains and fever two weeks after a sore throat and was treated for rheumatic fever elsewhere for two months with salicylates, coming here for a study in convalescence. He had shown, in addition to painful ankles, heat and tenderness over the knee, and painful elbows, a Grade 2 systolic murmur transmitted to the axilla. His P-R time was 0.16 second and fell in two weeks to 0.14 second. His ESR was 51 mm. in an hour on admission and fell to 14 mm. before discharge.

Our study had to do with the effect of activity on retention. Aside from extra amounts of ascorbic acid, the patient received no special treatment. The measured activity was the pedaling of a "bed bike" (a single wheel mounted on a platform on the end of the bed and previously described) for one minute twice a day, increasing by a minute daily.

Retentions increased markedly with exercise, but in the case of nitrogen retention declined when a point was reached at which he showed fatigue, in this case pedaling for 20 minutes. This correlates well with a point at which pulse pressure significantly increases.

He has been followed for three years and has had no recurrences and shows no evidence of carditis.

We feel that this case represents an example of the occurrence of a single bout of rheumatic fever in a well-nourished boy, terminating without sequelae. His gains in nitrogen and calcium are paralleled in a normal fashion by weight gains and give no suggestion of a previous deficit.

Case 6.—The patient, born Dec. 26, 1934, with metabolic study from May 1 through June 22, 1951, was a 16½-year-old boy who gave a history of rheumatic fever at the age of 7 followed by several exacerbations. At 14 he had a prolonged mastoid infection, at which time he showed evidence of well-established aortic and mitral lesions. At 15 there was a reactivation which responded rapidly to a short course (10 days) of corticotropin. Two months later he returned with fever, tachycardia, and signs of active carditis, his P-R time having increased from 0.15 to 0.20 second. He received another course of corticotropin from April 14, 1951, to May 2, 1951, starting with 60 units of corticotropin (Wilson) and changing to 48 units of corticotropin (ACTH, Armour) on April 29, with gradual withdrawal. He also received two Multicebrin tablets daily, containing 150 mg. of ascorbic acid. ESR fell from 23 mm. in an hour on April 13

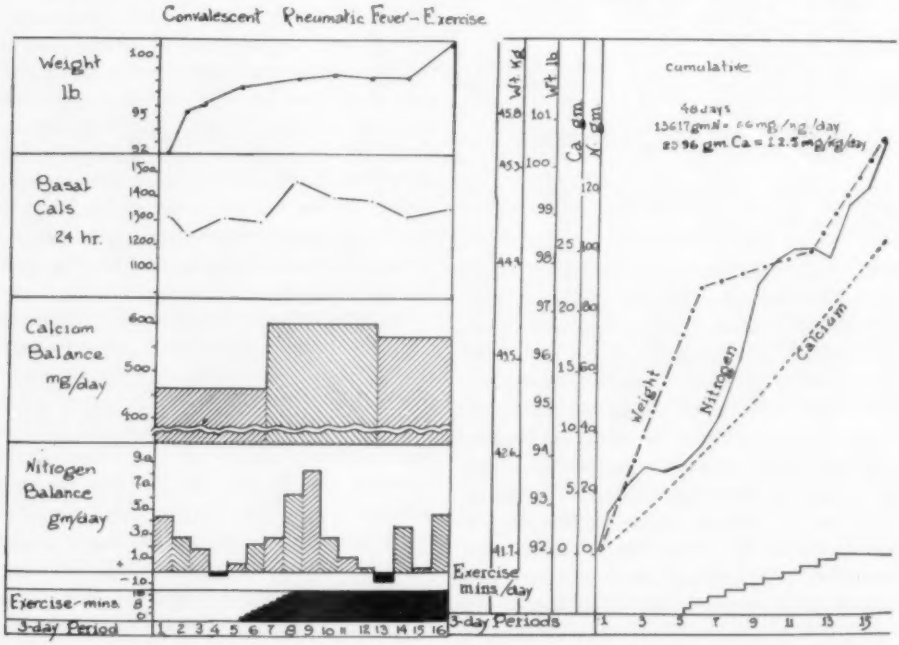


Fig. 6 (Case 5).—A boy, aged 12 years. Effect of activity on retention of nitrogen and calcium. Increased retention of both items follows the change from bed rest to exercise, but in the case of nitrogen retention falls when fatigue is produced. This occurred in 20 minutes of pedaling the bed bike.

TABLE 9 (Case 5).—*Balance Studies* *

Date	Nitrogen, Gm./Day					Calcium, Gm./Day					Basal Cal. 24 Hr.†	Wt., Kg.
	Av. Urine	Av. Stool	Intake	Balance	Accum.	Av. Urine	Av. Stool	Intake	Balance	Accum.		
5/14-5/31	13.55	1.17	16.70	1.98	35.61	0.170	1.425	1.886	0.461	8.298	1,288	44.22
6/1-6/15	12.99	1.23	14.22	0.00	100.62	0.169	1.216	1.902	0.606	17.388	1,428	44.67
6/16-6/30	13.55	1.14	17.06	2.37	136.17	0.178	1.151	1.905	0.576	25.528	1,332	45.91

* Weight of patient at beginning of observation, 41.84 kg.; height, 55⅛ in. Exercise was introduced on May 26, one minute twice daily, increasing by one minute daily.
† Average of basal determinations done at six-day intervals.

to 11 mm. in an hour on April 24 and 4 mm. in an hour on June 7. The variable of activity was introduced to measure its effect on the retention of nitrogen and calcium.

The balance study was started on the last three-day period of corticotropin therapy and continued for 54 days. Storages were high—3.42 gm. of nitrogen per day and 850 mg. of calcium per day. Moderate activity (walking about the ward) was followed by marked improvement in calcium storage, but as activity was increased nitrogen excretion rose. The storage of calcium at twice the usual level suggests previous deficits, which in this case could be understood as related to chronic infection of the upper respiratory tract including the mastoid.

Checked for three years, the patient was found on July 21, 1954, to be doing well and on full

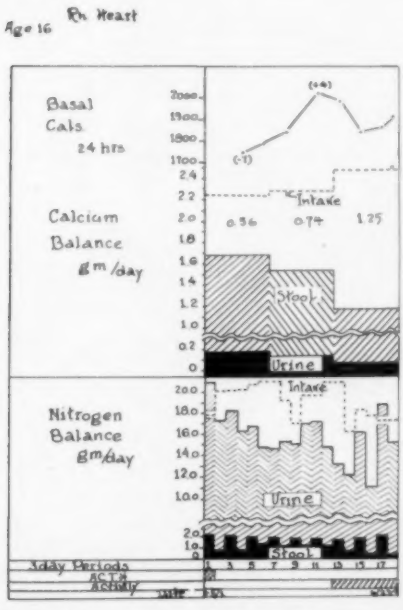


Fig. 7 (Case 6).—A boy, aged 16 years. Effect of activity on retention.

activity, though the signs of his valvular lesions were unchanged.

CASE 7.—A 10-year-old boy had a history of migratory joint pains, fever, and elevated ESR in June, 1947. He had had an excellent diet and normal growth, with a weight of 79½ lb. and height of 54 in. at the onset of illness. After five months of bedrest he was considered to show no residual carditis.

On Feb. 23, 1951, he had a recurrence of joint pain with swelling and fever three weeks after an attack of tonsillitis. He showed red swollen metatarsal joints; there was a Grade 2 systolic murmur, and ECG showed a partial AV block with a P-R time of 0.18 second.

He received corticotropin, 100 mg. daily, from Feb. 26 to March 27, with gradual withdrawal until completion on April 5. The P-R time fell to 0.14 second. He also received 100 mg. daily of ascorbic acid, 5 cc. of a proprietary multivitamin preparation (Homicebrin) daily, and on four occasions 0.6 gm. of acetylsalicylic acid for headache.

Metabolism studies were done in the convalescent period from April 20 to June 12. While the disease was clinically inactive, the ESR was 23 mm. in an hour.

The observation was concerned with noting (1) the degree of retention as a reflection of the size of the nitrogen pool and (2) the effect of exercise in gradually increasing amounts. This latter will be discussed separately. For two 18-day periods the retentions of nitrogen and calcium were identical with those we have reported for this age group in girls in the preadolescent age group and give no intimation of a previous deficit (Case 7, Table 11 and Fig. 8). Gain in weight parallels gain in nitrogen and calcium.

A four-year follow-up shows no evidence of carditis. Weight gain has been a problem as in so many of those treated in this manner; the weight rose to 164 lb. at 16½ years; with restricted calories it was reduced to 151 lb. at 17½ years. We feel that this case represents an example of rheumatic fever in the well-nourished boy terminating without residuals.

CASE 8.—A girl born April 29, 1938, with menarche in December, 1949, was one of a family of 10 children. Between the fifth and sixth preg-

TABLE 10 (Case 6*).—*Balance Observation, May 1 to June 23, 1951*

Date	Nitrogen, Gm./Day				Calcium, Gm./Day				B. M. R.		Basal Cal.	Weight		Diet Cal.	Comment
	Av. Urine	Av. Stool	Intake	Balance	Av. Urine	Av. Stool	Intake	Balance	Accum.	B.	W.	Lb.	Kg.		
5/1-5/3	18.78	2.13	17.92	−2.99	0.208	2.088	2.156	−0.140	−0.420	...	...	...	65.0	2,899	Corticotropin, 24 units on 5/1, 16 units on 5/2
5/4-5/6	16.54	0.82	20.10	+2.74	0.210	0.981	2.310	+1.119	.....	...	...	...	.....	3,000	
5/7-5/9	16.15	2.01	29.40	+7.47	0.134	1.915	2.370	+0.321	.....	...	...	...	.....	.....	
5/10-5/12	15.64	0.79	39.70	+14.27	0.177	0.836	2.290	+1.267	.....	...	...	...	.....	.....	
5/13-5/15	14.87	2.00	39.70	+3.83	0.160	1.947	2.130	+0.014	.....	−7	+6	145¾	66.384	.....	
5/16-5/18	13.57	1.34	21.00	+6.09	0.147	1.255	2.220	+0.818	+10.197	−7	+9	146	67.131	.....	
5/19-5/21	12.71	1.98	21.00	+6.31	0.127	1.892	2.430	+0.411	.....	...	...	...	.....	.....	
5/22-5/24	14.39	1.01	19.14	+3.74	0.164	1.076	2.163	+0.923	.....	−5	+11	148¾	67.471	.....	
5/25-5/27	13.31	1.86	17.04	+1.87	0.150	1.915	2.163	+0.098	.....	...	...	...	.....	.....	
5/28-5/30	16.02	1.04	19.56	+2.50	0.163	0.927	2.093	+1.063	.....	...	...	...	.....	.....	
5/31-6/2	15.44	1.72	19.56	+2.40	0.156	1.751	2.093	+0.186	.....	+4	+22	2,025	149	67.585	.....
6/3-6/5	13.89	1.02	20.97	+6.66	0.129	0.822	2.752	+1.801	+23.463	...	...	...	...	.....	.....
6/6-6/8	11.74	1.62	20.97	+7.61	0.109	1.877	2.752	+1.296	.....	+4	+21	1,989	148¾	67.471	.....
6/9-6/11	11.64	0.65	16.30	+4.01	0.110	0.699	2.498	+1.689	.....	...	...	...	.....	.....	Activity
6/12-6/14	14.37	1.94	18.42	+2.11	0.154	1.336	2.354	+0.804	.....	−4	+12	1,845	147½	67.018	increased
6/15-6/17	10.68	0.42	17.82	+6.73	0.099	0.695	2.354	+1.590	.....	...	...	...	.....	.....	on 6/11
6/18-6/20	16.29	2.19	17.44	+176.90	0.136	1.987	2.290	+0.167	.....	−3	+12	1,802	149½	67.811	.....
6/21-6/22	14.36	0.36	17.44	+185.06	0.123	0.399	2.290	+1.907	+45.912	−1	+15	1,912	150	68.039	.....

* Height, 66 in.

nancies, the mother had rheumatic fever; all five children born after this had the disease. Dietary history showed an adequate intake of meat, eggs, and milk.

At 11½ years this girl had chorea; she received fever therapy with seeming benefit and showed no carditis on discharge. Following this she had frequent sore throats and one attack of erythema marginata on Aug. 11, 1950. Hospitalized on Jan. 6, 1951, with a recurrence of chorea, dyspnea, orthopnea, and swollen ankles of three weeks' duration, she showed active carditis. She received a course of corticotropin (Wilson) 60 mg. daily from Jan. 10, 1951, to Jan. 22, 1951, with gradual withdrawal to Jan. 25, 1951. Following a flare-up of tachycardia and erythema multiforme, probably related to an acute throat infection, with a temperature of 102 F, another course of corticotropin was given, from Jan. 30, 1952, to Feb. 17, 1952, in addition to antibiotics for the throat infection. Balance studies were done from March 16, 1951, to June 30, 1951. A third course of corticotropin was initiated when there occurred a rise in pulse rate and temperature with evidence of early failure, on Feb. 6, 1951. In addition, she received 1.5 gm. of acetylsalicylic acid daily and two capsules of Multicebrin (150 mg. of ascorbic acid). Clinical response was good, with a fall in pulse rate and temperature and evidences of recovered compensation. A rise in pulse rate with gradual rise in ESR from 19 to 26 mm. in an hour led to a course of cortisone, 300 mg. daily, from May 26, 1951, through June 12, 1951.

Balance Study.—The patient was too ill for basal metabolic determinations throughout most of the study. There was a fall from approximately 0 to

CUMULATIVE BALANCE - 15 DAYS AFTER WITHDRAWL OF CORTISONE
♂, 14 yrs., Rh. Fever
Exercise
33 gm
35 gm
Wt. — — Wt. gain 54 days = 2.48 Kg
N. —— N. gain 54 days = 1.35 gm. = 2.5 gm./day
Ca ····· Ca. gain 54 days = 33 gm. = 0.6 gm./day
3 Day Periods

Fig. 8 (Case 7).—Balance study in a boy aged 14 years with excellent nutritional background, showing the expected normal storage of calcium and nitrogen with weight gain. The introduction of activity was followed by a plateau in weight with increased storage of nitrogen and calcium.

TABLE 11 (Case 7).—*Balance Observation April 2 to June 10, 1951, Fifteen Days After Withdrawal of Corticotropin*

Days, No.	Nitrogen, Gm./Day				Calcium, Gm./Day				Remarks
	Av. Urine	Av. Stool	Intake	Balance	Av. Urine	Av. Stool	Intake	Balance	
18	14.50	1.23	17.94	+2.21	0.350	1.294	2.207	+0.563	.....
18	13.56	1.37	17.50	+2.57	0.235	1.426	2.099	+0.439	.....
18	11.65	0.86	15.27	+2.74	0.200	1.101	2.185	+0.884	Exercise

—16% (Boothby), with a rebound on withdrawal of cortisone. Nitrogen excretion rose with corticotropin and cortisone, but in the second observation a negative balance was prevented by a rise in intake. Calcium was stored throughout and, aside from a slight increase in urinary output, was not significantly affected. The cumulative result of 117 days shows a storage of nitrogen and calcium comparable to the high normals we have noted in the adolescent at about the time of menarche—2.36 gm. N and 429 mg. Ca daily.

At the same time, the patient's weight at the end of 117 days of study was 152.4 gm. less than at the beginning. When such evidence of tissue reconstitution appears in the presence of a good dietary history, one would assume interference with the utilization, which in this case could well be accounted for by infected tonsils.

The patient has been followed through July 1, 1955, having been attending regular school without restriction. The only finding was a mitral systolic murmur which disappeared with exercise. She was overweight (130 lb., 64 in.), something we have found difficult to control in the hormone-treated cases.

This child's clinical course for two years was stormy and typical of an inability to react effectively to the disease process. Her course for the next three years has been highly satisfactory.

CASE 9.—A Negro girl aged 8 years had measles three weeks before admission. Four days before admission fever, sore throat, stiff neck, and painful joints developed. She had a past history of very frequent attacks of tonsillitis. Her diet was described as adequate. Temperature was 100.2 F but rose promptly to 103.6 F; pulse rate was 112; respirations, 22. Heart seemed enlarged and showed a Grade 3 systolic apical murmur with a crescendo quality. ECG showed a P-R time of 0.18 second. The cardiologist felt that there was evidence of active carditis. There was a complaint of tenderness in both ankles and some increase in heat. EST was 28 mm. in an hour; RBC, 2,790,000/cu. mm.; Hbg., 7.2 gm. per 100 cc. On the day after admission there was further complaint of pain in the knees and chest. She received for five days 20 mg. of

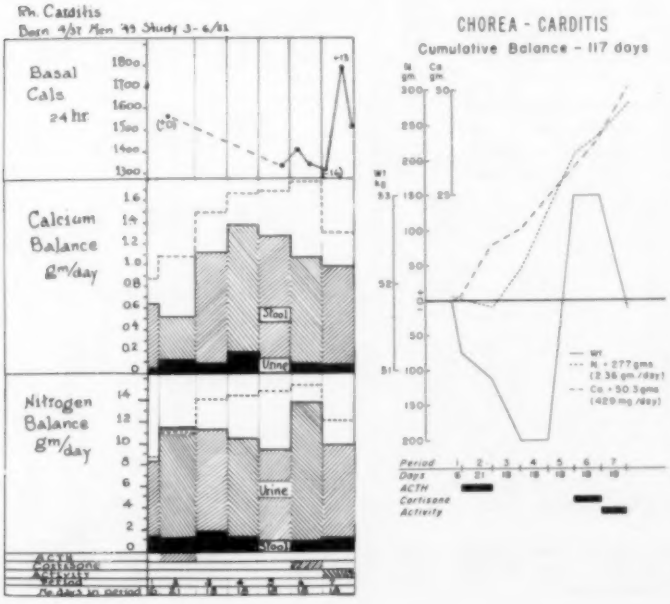


Fig. 9 (Case 8).—In a girl aged 14 years, two years after menarche, the net result of one course of corticotropin and one of cortisone was the addition to the tissues of 277.08 gm. of nitrogen and 50.298 gm. of calcium, with weight at the end of the observation identical with that at the beginning.

corticotropin (Wilson), 1.68 gm. of acetylsalicylic acid (weight of patient, 54 lb.), and 15 cc. of Homicebrin, containing 90 mg. of ascorbic acid. Relief of all symptoms was prompt and was sustained on discontinuance of therapy. She has been followed for three years and shows no evidence of carditis.

The balance study from June 25, 1950, through July 7, 1950, showed very large retentions both during and after discontinuance of the hormones and salicylates while weight was being lost, a phenomenon typical of previous deficits. With a history of an adequate diet, the most likely explanation for the deficit can be found in the severely chronically infected tonsils.

CASE 10.—A 12-year-old girl, admitted on Feb. 7, 1955, became ill two weeks before admission with fever, fatigue, anorexia, and painful swollen ankles, knees, and elbow. She was youngest of 10 children; her history revealed a minimum intake of milk and a definite aversion to eggs.

She was poorly nourished (height, 56 in.; weight, 62 lb.; B-4 Wetzel). The temperature was 101.8 F; pulse rate, 120, and respirations, 24. The ankles, knees, and right elbow were swollen, hot, and painful to touch. There was a Grade 2 systolic murmur and some enlargement of the heart by x-ray but a normal ECG. Sedimentation rate was 38 mm. in an hour.

The patient received 3.6 gm. of acetylsalicylic acid daily for three days, after which it was reduced to 2.4 gm. for four days and then to 1.8 gm. on Feb. 25, 1955. The temperature fell in 28 hours; the sedimentation rate, in 2 weeks.

Nitrogen balance study was run for 42 days, beginning 1 week after admission, when the temperature had been normal for 5 days but while the patient was still receiving salicylates.

In two periods there was good nitrogen storage; in the others she was just in balance, and in two the balance was negative. The cumulative storage was 0.42 gm. a day. There was a fall in basal

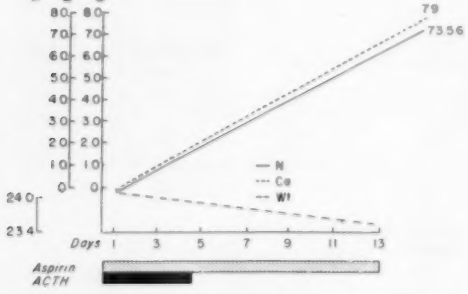


Fig. 10 (Case 9).—A girl, aged 8 years. Large retentions with weight loss probably reflect deficits attributable to chronically infected tonsils.

TABLE 12 (Case 8).—*Balance Observation March 6 to June 30, 1951* *

Period No.	Days, No.	Nitrogen, Gm./Day				Calcium, Gm./Day				B. M. R.		RQ†	Basal Cal.	Kg.	Diet Cal.
		Av. Urine	Av. Stool	Intake	Balance	Av. Urine	Av. Stool	Intake	Balance	Accum.	B.	W.			
1	6	6.92	1.41	8.69	+0.35	0.048	0.598	0.853	+0.207	+1.242	....	....	....	.....	2,200
2	21	10.19	1.19	11.00	−0.38	0.119	0.887	1.084	+0.578	+13.380	0	+15	0.74	1,562	51.2	.....
3	18	9.61	1.64	13.95	+2.70	0.098	1.021	1.402	+0.378	+20.094	....	....	....	.....	50.9	.....
4	18	9.22	1.08	14.23	+3.93	0.182	1.206	1.651	+0.263	+24.825	....	....	....	.....	50.2	.....
5	18	8.56	0.89	14.73	+5.29	0.111	1.153	1.665	+0.401	+32.046	−14	−2	0.74	1,344	53.0	.....
6	18	12.75	0.94	15.35	+1.66	0.091	0.985	1.765	+0.689	+44.448	−14	−1	0.80	1,355	53.0	.....
7	18	8.84	1.02	12.00	+2.14	0.077	0.899	1.301	+0.325	+50.998	−5	+21	0.77	1,655	51.7	.....

* Menarche in December, 1949.
† RQ, respiratory quotient, CO_2/O_2.

TABLE 13 (Case 9).—*Balance Observation June 25 to July 25, 1950*

3-Day Period No.	Date	Nitrogen, Gm./Day					Calcium, Gm./Day					B. M. R.		Basal Cal.	Weight		Ht., In.	Diet Cal.	Comment
		Av. Urine	Av. Stool	Intake	Balance	Accum.	Av. Urine	Av. Stool	Intake	Balance	Accum.	B.	W.		Lb.	Kg.			
1	6/25-6/27	6.01	0.78	13.20	+6.41	+19.23	0.110	0.913	1.520	+0.497	1.491	+4	+22	1,104	53¾	24.2	53¼	2,000	Corticotropin, 6/25-6/28
2	6/28-6/30	5.50	0.66	13.00	+6.84	+39.75	0.150	1.043	1.460	+0.267	2.292	...	....	.....	....	....	....	.....	
3	7/1-7/3	8.71	0.27	13.00	+4.02	+51.81	0.248	0.591	1.460	+0.621	4.155	...	....	.....	....	...	....	.....	.....
4	7/4-7/6	6.63	0.84	13.00	+5.53	+68.40	0.167	1.366	1.500	—0.033	4.056	+1	+5	1,658	52	23.5	50¾	.....	.....
5	7/7	7.84	0.00	13.00	+5.16	+73.56	0.209	0.000	1.500	+1.291	7.929	...	....	.....	....	....	....	.....	.....
Av.		7.17	0.44	13.00	+5.39	.....	0.193	0.750	1.480	+0.537	.....	...	....	.....	....	....	....	.....	.....

TABLE 14 (Case 10).—*Balance Observation Feb. 14 to March 27*

6-Day Period No.	Date	Nitrogen, Gm./Day								B. M. R.		RQ	24 Hr. Basal Cal.	Weight		Ht., In.	Diet Cal.
		6-Day Urine	Av. Urine	Av. Stool	Output	Intake	Balance	3-Day	Accum.	B.	W.			Lb.	Kg.		
1	2/14-19	51.23	8.54	0.44	8.98	9.80	+0.82	+4.92	+4.92	+5	+10	0.83	1,264	62¾	28.51	56	1,500
2	2/20-25	44.71	7.45	0.33	7.78	9.94	+2.16	+12.96	+17.88	....	....	....	.....	....	.....	..	.....
3	2/26-3/3	51.48	8.58	0.83	9.41	9.69	+0.28	+1.68	+19.56	—19	—17	0.83	909	60¼	27.39	56	.....
4	3/4-9	39.99	6.66	1.30	7.96	9.24	+1.28	+7.68	+27.24	....	....	....	.....	....	.....	..	.....
5	3/10-15	50.99	8.49	1.44	9.93	10.15	+0.22	+1.32	+28.56	—13	—16	0.84	974	61¾	27.96	56¼	.....
6	3/16-21	48.75	8.12	1.31	9.43	8.98	—0.45	—2.70	+25.86	—15	—11	0.88	972	62¾	28.51	56	.....
7	3/22-27	54.69	9.11	1.25	10.36	8.95	—1.35	—7.86	+18.00	—15	—11	0.85	979	64½	29.87	56¼	.....
								0.43 gm./Day									

TABLE 15 (Case 11).—*Balance Observation* *

Date	Nitrogen, Gm./Day					Calcium, Gm./Day					B. M. R.		Basal Cal.	Kg.	Diet Cal.
	Av. Urine	Av. Stool	Intake	Balance	Accum.	Av. Urine	Av. Stool	Intake	Balance	Accum.	B.	W.			
7/6-7/8	5.52	0.91	11.97	+5.54	+16.62	0.099	1.853	1.583	—0.369	—1.107	+1	+12	1,540	42.964	1,800
7/9-7/11	5.26	0.76	12 33	+6.31	+35.55	0.132	1.428	1.547	—0.013	.....	...	....	.....	.....	.....
7/12-7/14	7.91	0.74	13.05	+4.40	+48.75	0.165	1.363	1.457	—0.071	—1.359	+8	+20	1,656	42.751	.....
7/15-7/17	9.89	1.02	13.82	+2.91	+57.48	0.277	1.817	1.435	—0.609	.....	...	.....	.....	.....	.....
7/18-7/20	7.24	1.25	14.54	+6.05	+75.63	0.156	1.720	1.503	—0.343	—4.215	+1	+11	1,538	42.978	.....
7/21-7/23	8.78	1.16	13.64	+3.76	+86.91	0.186	1.660	1.485	—0.361	.....	...	....	.....	.....	.....
7/24-7/26	6.78	0.79	13.67	+6.10	+105.21	0.112	1.415	1.489	—0.038	—5.412	—1	+9	1,514	42.978	.....

* Height, 53¼ in.; weight, 94½ lb.

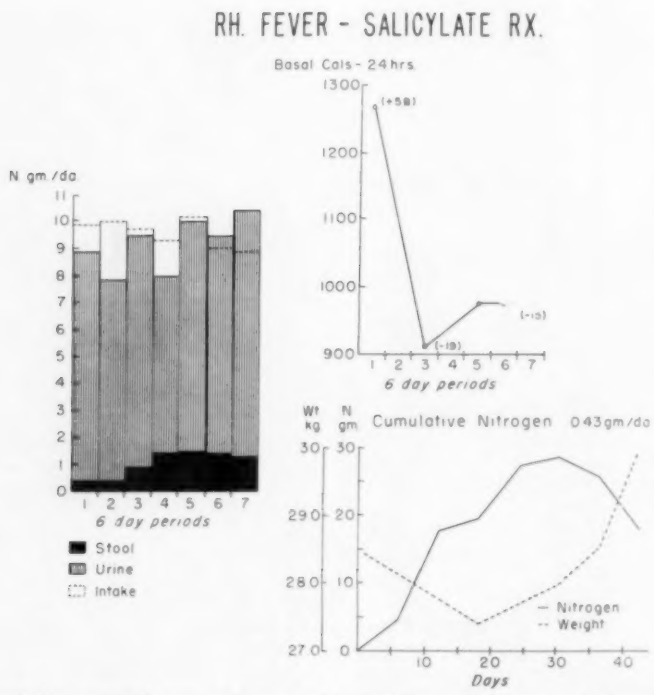


Fig. 11 (Case 10).—A fall in basal metabolism comparable to that seen with cortisone and referable to drop in temperature occurred in this girl treated with salicylates. None of the other effects seen with cortisone—increase in intake or initial loss followed by large gains of nitrogen—are seen here. The net result of three weeks was a gain of 0.43 gm. of nitrogen per day.

calories comparable to that seen with cortisone. There was not noted any large loss of nitrogen nor any increase in intake; in fact, food had constantly to be urged.

Case 11.—A boy born Dec. 15, 1942, with onset of rheumatic fever on May 3, 1951, was studied in July, 1951. There was a family history of allergy and a past history of asthma, which started when the patient was 3 years old.

The diet had been low in protein, high in carbohydrate, and adequate in vitamins C and D. The patient had always been overweight (89 lb. and 53 in.; A4 Wetzel). Present illness began as typical attack of rheumatic fever, with joint pains and heart involvement one month after a respiratory infection. The patient was admitted with early failure, digitalized, and placed on corticotropin for 18 days followed by cortisone for 28 days.

During bed rest in convalescence, when the sedimentation rate was still elevated, he received, in addition to the standard diet, 300 mg. of ascorbic acid daily, 5 cc. of Homicebrin, and a preparation of molybdenum oxide and ferrous sulfate (Mol-Iron). In the 21-day balance study, nitrogen storage was extremely high (5 gm. a day). Part of this probably resulted from the phenomenon usual after withdrawal of cortisone, though there was an interval of 18 days between withdrawal and the balance study. We should interpret it as the type of balance study noted when an obese child previously on a high-carbohydrate diet is put on one adequate in protein. In the final three-day period, exercise was introduced (pedaling a wheel for one minute, increasing by a minute daily), and, while the period is too short for significance as regards fecal calcium, it is to be noted that urinary nitrogen and calcium both fell. The calcium balance was negative throughout.

Recurrence of rheumatic fever 15 months later was again treated with cortisone for 15 days. Fifteen months after this, examination was negative except for obesity. Four year follow-up in July, 1955, shows normal cardiac findings.

SUMMARY AND CONCLUSIONS

The outcome in rheumatic fever is influenced by the nutritional state.

There is a high correlation between a favorable outcome and an advantageous channel on the Wetzel grid.

Metabolic studies bring out the existence of deficits in nitrogen and calcium as judged by the high retention of these substances with flat or declining weight curves.

Prolonged bed rest influences adversely the retention of nitrogen and calcium; very moderate degrees of activity offset this.

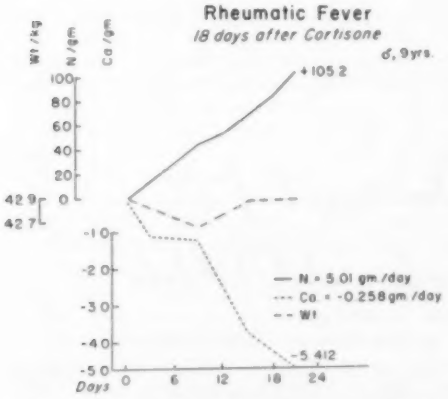


Fig. 12 (Case 11).—This boy was overweight and gave a history of a high-carbohydrate low-protein intake. On the standard diet, containing 15% of the calories in protein, he gained 5.01 gm. of nitrogen a day while losing weight. The high storage of nitrogen and coincident loss of weight are typical of results in a child previously on a diet inadequate in protein when he is given adequate protein. The loss of calcium here is not completely understood; complete bed rest played a role, but it is also true that when nitrogen storage is very large, such as when induced by testosterone, calcium storage may reciprocally fall.

On a regimen combining cortisone or corticotropin, salicylates, and ascorbic acid the outcome in rheumatic fever has been significantly better than on previous regimens, though this conclusion must be qualified by the recognition that there has been a decline in the severity of the disease in the past 10 years.

In the management of the child with rheumatic fever, consideration should be given to all of the factors which influence nutrition, as judged by the retention of nitrogen and calcium, the dietary intake, focal infection, hormones, rest, and activity.

REFERENCES

1. Glover, J. A.: Milroy Lectures on Incidence of Rheumatic Diseases: Incidence of Acute Rheumatism, Lancet **1**:499-505 (March 8) 1930.

2. Marshall, R.: Review of 180 Children Suffering from Rheumatism, Chorea and Carditis, Arch. Dis. Child. **3**:28-38 (Feb.) 1928.

3. Warner, E. C., and Winterton, F. G.: A Dietetic Study of Juvenile Rheumatic Disease, Quart. J. Med. **4**:227-245 (July) 1935.

4. Peete, D. C.: Rheumatic Fever: Diet as a Predisposing Factor, Ann. Int. Med. **21**:44-57 (July) 1944.

5. Coburn, A. F., and Moore, L. V.: Nutrition as a Conditioning Factor in Rheumatic State, Am. J. Dis. Child. **65**:744-756 (May) 1943.

6. Wallis, A. D.: Dietary Eggs and Rheumatic Fever, Am. J. M. Sc. **227**:167-170 (Feb.) 1954.

7. Johnston, J. A.: Nutritional Studies in Adolescent Girls and Their Relation to Tuberculosis, Springfield, Ill., Charles C Thomas, Publisher, 1953.

8. Kahn, L.; Brown, G., and Goldring, D.: Wetzel Grid Analysis of Rheumatic Children, J. Pediat. **41**:47-52 (July) 1952.

9. Higgons, R. A.; Hyde, G. M., and Malsch, M. L.: Five Hundred Patient Years of Rheumatic Disease in Children, New York J. Med. **51**:1143-1151 (May 1) 1951.

10. Wilson, M. G.: Rheumatic Fever, New York, Harvard University Press, Commonwealth Fund, 1940.

11. Johnston, J. A., and Maroney, J. W.: Focal Infection and Metabolism: Effect of Removal of Tonsils and Adenoids on Nitrogen Balance and Basal Metabolism, J. Pediat. **12**:563-570 (May) 1938.

12. Johnston, J. A., and Watkins, T.: Tonsillectomy and Adenoidectomy: A Re-Evaluation of Results, J. Pediat. **44**:127-133 (Feb.) 1954.

13. Bray, B. M.: Nitrogen Metabolism in West African Children, Brit. J. Nutrition **7**:3-13, 1953.

14. Johnston, J. A., and Sweeney, M. J.: Factors Affecting Retention of Nitrogen and Calcium in Period of Growth: IX. Corticotropin (ACTH), A. M. A. Am. J. Dis. Child. **82**:685-701 (Dec.) 1951.

15. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in Period of Growth: IV. Effect of Estrogen, Am. J. Dis. Child. **62**: 708-715 (Oct.) 1941.

16. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in Period of Growth: VII. Effect of Methyl Testosterone, Am. J. Dis. Child. **74**:52-57 (July) 1947.

17. Wallace, H. M., and Rich, H.: Changing Status of Rheumatic Fever and Rheumatic Heart Disease in Children and Youth, A. M. A. Am. J. Dis. Child. **89**:7-14 (Jan.) 1955.

18. Holt, K. S.; Illingworth, R. S.; Lorber, J., and Rendle-Short, J.: Cortisone and Salicylates in Rheumatic Fever, Lancet **2**:1144-1148 (Dec. 4) 1954.

19. Done, A. K.; Ely, R. S.; Ainger, L. E.; Seely, J. R., and Kelley, V. C.: Therapy of Acute Rheumatic Fever, Pediatrics **15**:522-536 (May) 1955.

20. Houser, H. B.; Clark, E. J., and Stolzer, B. L.: Comparative Effects of Aspirin, ACTH and Cortisone on the Acute Courses of Rheumatic Fever in Young Adult Males, Am. J. Med. **16**: 168-180 (Feb.) 1954.

Chlorpromazine in the Treatment of Severe Emotional Disorders of Children

BRIAN R. HUNT, B.M., B.Ch. (Oxon.)
THOMAS FRANK, M.D.
and
THADDEUS P. KRUSH, M.D., Waltham, Mass.

During the last 18 months there has been much interest in the use of chlorpromazine (Thorazine) in the treatment of psychiatric conditions. The many reports * from the American literature refer primarily to its use with disturbed adults. As the drug had been shown to reduce activity in all mental states, with the production of a state of psychic indifference,† interest was aroused in assessing its usefulness in the treatment of emotionally disturbed children. The more recent reports ‡ on the use of chlorpromazine in children refer primarily to its effect on the overactive, aggressive child. The present study was undertaken as a survey of the effects of chlorpromazine on a wide range of severe emotional disturbances. Within the limitations of our material we have tried to delineate the clinical indications for the use of the drug in children, as well as the emotional complications arising from it.

Received for publication Aug. 17, 1955.

The chlorpromazine used in this study was supplied as Thorazine by Smith, Kline & French Laboratories, Philiadelphia.

* References 1-5.

† Reference 6 and Freed, H.: Treatment of Hyperkinetic Emotionally Disturbed Children with Prolonged Administration of Chlorpromazine, read before the American Psychiatric Association, Atlantic City, N. J., May 10, 1955.

‡ Reference 7 and Freed, H.: Treatment of Hyperkinetic Emotionally Disturbed Children with Prolonged Administration of Chlorpromazine, read before the American Psychiatric Association, Atlantic City, N. J., May 10, 1955.

MATERIAL

The study was conducted at the Gaebler Children's Unit of the Metropolitan State Hospital, Waltham, Mass. This unit, located away from the adult hospital, functions as a residential treatment center for those children whose emotional disturbance, of whatever type, is of such severity as to make it impossible for them to live in the community or other types of residential centers available. The material used is summarized in Table 1. For the purpose of this study, the diagnosis was made on the basis of the most prominent clinical feature, with other features noted as secondary. To clarify this point, representative patient histories are included under each category. The duration of the patient's hospitalization prior to the study ranged from eight years to six months; most were hospitalized one to two years. Many patients had experienced varying periods of psychotherapy, but this was not felt to be an important variable in evaluating the immediate effect of the drug. The children were allowed home visits and visitors during the trial with chlorpromazine in the same manner as prior to its use. Those patients having known epilepsy were continued on their regular anti-convulsant medication in addition to chlorpromazine.

METHOD

This study is focused on the first month that the patient received the medication; many continued with the drug after the study. Eleven of the fifty-eight patients—five boys and six girls—served as a pilot group, receiving only the drug, so that we could establish effective dosage levels and gain experience in the event that side-effects supervened. The remaining 47 patients—40 boys and 7 girls—were divided into two groups, closely matched as to age and diagnosis. One group was placed on chlorpromazine and one on placebo. After one month, the group started on placebo was switched

to chlorpromazine and vice versa. The active drug and placebo were, of course, identical in appearance. There was no tapering off of medication. It might be noted that some exacerbation of previous symptomatology occurred with the sudden shifting to placebo, but this lasted only two to three days.

Evaluation of behavior change was based on weekly reports from the counsellors, occupational therapy workers, school teachers, and attending psychiatrists. These workers did not know whether a patient was receiving placebo or drug. They were requested to give as full a report as possible on their observations of the child's behavior, including verbal behavior, paying particular attention to any change. The observations were made during the course of their routine activities in order to keep at a minimum the effects of extra attention given to the children. These reports were initiated three weeks prior to the beginning of medication, to establish a base-line of behavior. So far as possible, knowledge of anticipated change was withheld from the observers.

The drug was presented to the children as "a way of helping you to get along better." During the first days, the idea got around that this was actually a vitamin "to pep you up," and a considerable number became more active and excitable, whether on drug or placebo. On the second and third days, the idea changed to the pills being a "sleeping medicine," and many patients spent much of the day either asleep or dozing, regardless of whether receiving drug or placebo. After four or five days the administration of the medication (drug or placebo) was accepted as a part of hospital routine. Two patients refused to take the medication orally, and so they received the same dosage intramuscularly until they acquiesced. Some of the children, particularly the delinquent group, became very adept at hiding tablets in the mouth or the back of the throat; they pretended to swallow but later spat out the medication. This problem was handled by giving the drug in liquid form; this form was also used for patients who had difficulty in swallowing tablets for reasons other than resistance.

The initial doses used were 75 mg. per day for those uder 12 years and 150 mg. per day for older or more disturbed children. These were divided into three equal doses and increased or decreased as indicated by clinical change.

OBSERVATIONS

Following the first 2 to 10 days on the drug, there were complaints from nearly all children that they felt sleepy. This disappeared without change of dose as the drug was continued. In a few cases it was necessary to raise the dose after two weeks of medication, but there was no serious difficulty from tolerance in this short-term study.

TABLE 1.—*Classification of Disorder and Result of Treatment in Fifty-Eight Children Given Chlorpromazine*

	Patients, No.						
	Chronic Schiz.	Subacute Schiz.	Acute Schiz.	Behavior Disorder	Delinquent	Organic Damage	Total
Total in each group	17	6	3	16	9	7	58
Degree of improvement							
Slight	6	1	..	2	1	..	10
Mild	5	1	..	7	..	3	16
Moderate	4	2	1	2	2	1	12
Extensive	1	..	2	2	1	..	6
Inconclusive	..	2	..	1	1	..	4
No change	1	..	..	2	1	1	5
Worse	..	..	..	..	3	2	5

There was great variability in individual response to medication. Many of the older children on medication complained of "shaky feeling" and vague feelings of dizziness, unreality, or "swimminess." These somatic sensations aroused considerable secondary anxiety and were thought to be due to the initial large dose. This secondary anxiety can be prevented by giving small doses in the first few days and increasing medication gradually to the required therapeutic dose. The individual variation in the size of the therapeutic dose is best illustrated by the daily requirements of two boys: An 8-year-old weighing 40 kg. needed 450 mg. per day; a 14-year-old weighing 60 kg. was very sleepy on 75 mg. per day.

Some of the effects of placebo have already been mentioned. A few of the children continued to complain of feeling tired after changing from drug to placebo; none of

these patients were psychotic, and all had shown only slight or mild degree of change and little pretreatment hyperactivity. One schizophrenic patient with marked oral delusions became acutely disturbed when on placebo, and administration of the drug had to be resumed to control his hyperactivity and assaultiveness. In the majority of patients the response to placebo highlighted the beneficial effects of chlorpromazine.

The degree of improvement was judged to be slight, mild, moderate, or extensive. The estimated change was relative to the pretreatment behavior and gives no indication of the improvement still required for the patient to be considered "recovered." For ease of description and discussion, the children are divided into broad diagnostic categories. These categories are clarified and the observations in each group discussed in the following paragraphs. The duration of psychosis, age, dosage, and other details are summarized for each group in Tables 2 to 7, respectively.

TABLE 2.—*Chronic Schizophrenic Group*

Degree of Improvement	Patients, No.	Duration of Psychosis, Yr.	Ages, Yr.	Patients in Therapy, No.	Dose, Mg./Day
Slight	6	5-10 (av. 8.2)	12-14 (av. 12.8)	1	100-150
Mild	5	4-12 (av. 7)	10-14 (av. 12.2)	1	150
Moderate	4	1-5 (av. 3.6)	8-15 (av. 10.2)	2	150-300
Extensive	1	6	15	0	150-300
No change	1	8	12	0	75-150

CHRONIC SCHIZOPHRENIC GROUP (TABLE 2)

There were 17 patients classified as chronic schizophrenic. The following brief history typifies the children in this group.

A boy, now 12 years old, was admitted to the hospital at the age of 6 years. The neonatal period was normal, as was early maturation. The mother stated that "I started crying about him nine hours after he was born, and have cried about him ever since." He became disturbed when weaning was attempted at 7 months, and bottles were only removed at the age of 2 years. At the age of 18 months he developed an intense curiosity about his sister's body, at which time the parents had to hide all scissors and knives because he was literally trying to cut his penis off. At the age of 2½ years he had an operation without any psychological preparation, and at the same time a visiting maternal grandmother also had an operation and died shortly afterward. With the maternal grandmother's death the mother went into a period of mourning, and a noticeable change in the boy began at about this time. He progressively gave up speech and became more bizarre in his behavior. At the age of 3 years he would spend much time sitting and staring into space, or walking up and down and crying pitifully and agonizingly, while seemingly completely oblivious of everyone. He did not care for children and shied away from adults. At other times he would tend to be restless and hyperactive. At the age of 5 years he became self-destructive, and this increased to an extent that necessitated his admission to the hospital by the age of 6 years.

During his time in hospital he has remained mute, seclusive, untidy, and unable to care for his needs.

The father is described as a simple man who in his early childhood was thought to be "a little queer." The mother showed marked perfectionistic and obsessional trends and related to the boy with alternate aggression and seduction.

Of the 17 patients having chronic schizophrenia, 1 showed extensive improvement; 15, slight to moderate improvement; 1, no change. Improvement was reflected by changes in psychomotor activity, awareness of people and objects in the environment, and social integration, including changes in play patterns.

The patient showing extensive improvement was a girl who improved from a mute withdrawal, punctuated by occassional impulsive episodes, to her becoming a fringe member of a group with whom she would now initiate brief conversations.

The most marked change in the 15 patients was slight to moderate improvement in psychomotor activity. Twelve patients previously hyperactive became less so. Three patients, previously very withdrawn, became more active on medication. In 11 patients there was improvement in awareness of their

environment, and 9 showed improved social integration.

The therapists, who were "blind" as to which drug was active, remarked on the rapid progress made by four children on chlorpromazine when seen in individual psychotherapy. They particularly felt that that there was much improved integration of self.

Comment.—Chlorpromazine appears to be of definite value in the treatment of chronic schizophrenia in children. The results are comparable to those obtained in similar states in adults.[8] In our patients the value of chlorpromazine appears to be to control hyperactivity; to overcome the barrier of being isolated and withdrawn; to act as an adjuvant to psychotherapy by increasing awareness and social integration.

TABLE 3.—*Subacute and Borderline Schizophrenic Group*

Degree of Improvement	Patients, No.	Duration of Psychosis, Yr.	Ages, Yr.	Patients in Therapy, No.	Dose, Mg./Day
Slight.....	1	3	15	0	150
Mild.....	1	1-2	12	0	150
Moderate.....	2	1-2	13	1	75
Extensive.....	0	...	..	..	...
Inconclusive..	2	1-2	13 & 14	1	150

The degree of improvement in many patients appeared to be directly proportional to the adequacy of adjustment during the first three years of life. Reappearance of early symptoms leading to extremely infantile behavior prior to improvement was noted, particularly where onset of original illness had been rapid. An improvement response appeared to be dependent on three interrelated variables: adequacy of adjustment in the first three years of life; rapidity of onset of schizophrenia, and residual potential ability of the ego.

SUBACUTE AND BORDERLINE SCHIZOPHRENIC GROUP (TABLE 3)

This group consisted of six patients considered to have borderline or subacute schizophrenia.

A boy, now 13 years old, was admitted to the hospital at the age of 11 years. He was an illegitimate child and unwanted. His mother went to work when he was 7 months old and gave his care to an overly protective, rigid, compulsive grandmother. His early neurological development is believed to have been normal. When he was one year old his mother died. From the age of 5 years he had difficulty getting along with other children, and at that time he first started stealing money. Since then he had showed increased lying, stealing, aggressiveness, temper tantrums, and some running away. When he was 7 years old his grandfather died, and the boy was very upset. At the age of 8 years he turned on the gas in two attempts to kill his grandmother, and on other occasions he would knock her down. He was then placed in a foster home, where he was described as lacking warmth and being unable to relate to children or adults. His admission to hospital at the age of 11 was precipitated when the patient threatened attacking an elderly man at the behest of "just voices." In the following nine months the "voices" apparently disappeared, but he continued to have aggressiveness and temper tantrums. Again at the age of 12 years there was a period during which he spoke of a voice telling him to do things and said that his dead grandfather sometimes visited him and put a cold hand on his neck.

Of the six patients in this group, four showed improvement, becoming less hyperactive and more easily managed, with increased ability for social integration. With one exception, they also showed more awareness of and responsiveness to their environment. The exception, a 13-year-old girl, otherwise showed moderate improvement but had recurrent depressions when on the drug.

Comment.—In this group, chlorpromazine medication appears to be of most value in the control of hyperactivity and the improvement of social integration. The importance of the latent strength of the ego is again emphasized by the relative lack of improvement in the person with mental deficiency.

Of more interest here is the inconclusive effect in the two patients showing much withdrawal, since the drug reduced withdrawal in chronic schizophrenia. In spite of poor emotional environment, both these patients had shown a fair degree of adjustment up to the time of the psychotic disturbance; each had had a period of relative ego strength. Both patients showed evidence of extreme

fear underlying their withdrawal. This fear of annihilation was considered too intense to be sufficiently modified by chlorpromazine. It remains to be seen whether continuation of a high dosage for a much longer time will be of value in this type of patient.

Acute Schizophrenic Group (Table 4)

Only three cases were considered to be acute schizophrenia. The following history is an example.

A girl, now 14 years old, had been admitted at the age of 13 years. Early development was normal, and she seems to have been fairly well adjusted until the age of 13 years. She had experienced a very difficult relationship with her father, who seemed to pick on this girl more than on the other children. He had a long court record with arrest for drunkenness and lewd behavior, and it is suspected that some of his attacks on the girl had a strong sexual connotation. The father left the home six months prior to the girl's psychotic breakdown. The mother was a strict disciplinarian, who felt the home would have been a perfect one had it not been for her husband.

Table 4.—*Acute Schizophrenic Group*

Degree of Improvement	Patients, No.	Duration of Psychosis, Yr.	Ages, Yr.	Patients in Therapy, No.	Dose, Mg./Day
Moderate..	1	1	14	1	300
Extensive..	2	1	15	1	75 & 600*

* Additional reserpine medication was given to this patient.

At the age of 13 years, when on a picnic, the girl suddenly fainted. On the following day she became extremely frightened and quite uncontrollable and kept saying "I see him coming." This extreme fear continued through much of the early months of her hospitalization. Auditory and visual hallucinations regarding her father attacking her with a knife became increasingly more prominent. It was at this time that medication was started.

Of these three patients with acute schizophrenia, two were considered to have typical acute breakdowns in adolescence with hallucinations and delusions. In both, the hallucinations and delusions disappeared very early following medication, whereas they had persisted during three to six months of hospitalization prior to medication. The third patient exhibited severe catatonia, showing alternate episodes of stupor and excitement and tending to relapse at approximately three- to five-week intervals. The first two relapses followed courses of electroshock therapy. The following three relapses occurred on chlorpromazine, and each was ended by increase in dosage. Following the final relapse this boy was started on 2 mg. of reserpine (Rau-Sed) daily in addition to the chlorpromazine. Whereas the recovery from relapses under shock therapy needed two to three weeks, under chlorpromazine signs of recovery were evident in two days. Following the addition of reserpine to his medication, improvement was rapid and maintained. Two patients were in individual psychotherapy. Both therapists noted improvements.

Comment.—The disappearance of hallucinations and delusions was striking. In the ward setting the patients were much calmer and more easily handled and showed improved social integration. One of these patients had a high level of anxiety prior to medication. Although the verbal content during medication revealed many apprehensions, there was an absence of other physiological evidence of anxiety in facial expression, voice, and posture. This was associated with the usual reduction of motor activity. A similar effect on severe anxiety in psychotic and prepsychotic persons has been noted in other patients, who are often described as showing "lethargic anxiety." A considerable part of the effect of chlorpromazine appears to be the reduction of the autonomic manifestations of anxiety.

Behavior Disorder Group (Table 5)

This group included 16 children whose conflicts were primarily manifested in terms of behavior, but not of the type usually considered delinquent. Their behavior showed varying degrees and combinations of hyperactivity, aggressiveness, and anxiety. The following patient is typical of this group.

A boy, now 10 years old, was admitted at the age of 9 years. Early development was normal. The father left the home when the boy was one year old, and the mother had to go out to work.

TABLE 5.—*Behavior Disorder Group*

Degree of Improvement	Patients, No.	Ages, Yr.	Patients in Therapy, No.	Dose, Mg./Day
Slight.....	2	10 & 11	0	75 & 150
Mild.....	7	8-14 (av. 11.4)	4	75-150
Moderate.....	2	10 & 14	1	150-300
Extensive.....	2	9 & 10	1	150-225
Inconclusive...	1	9	0	75
No change.....	2	14 & 15	0	75

The boy was left with maternal grandparents, but they refused to keep him after he was 2 years old because of aggressive, hyperactive behavior. Placement in several foster homes was tried, but similar behavior precipitated his removal. When he was 5 years old his mother remarried and took the patient back to live with her. His aggressive, hyperactive behavior continued with increasing severity, culminating in his admission to the hospital. In spite of his great hyperactivity and distractability the boy scored an I. Q. of 86. There was no clear evidence of any organic factor involved in his behavior. In hospital he was in continuous activity and appeared incapable of being near a younger child without hitting or kicking him without any provocation. The hyperactivity was so great that it was feared that his continual running might lead to exhaustion.

Of these 16 patients, the 2 showing only slight change were the least hyperactive of the 13 cases showing improvement. Their change on medication was better social integration. Both had an organic component in their disorder; one suffered latent idiopathic epilepsy, and one, moderate mental retardation.

The remaining 11 patients revealed reduced hyperactivity and aggression with better social integration. Three of these patients had an organic component of diffuse type: "minimal brain damage." The four patients showing moderate and extensive improvement were those with the greatest hyperactivity prior to medication.

Six of the thirteen patients who improved became moderately depressed while on the drug, despite the absence of overt depression prior to medication.

The six therapists associated with the behavior disorder group were uncertain of the advantages of chlorpromazine as judged from observations in the therapeutic sessions.

Comment.—Chlorpromazine appeared to be remarkably effective in controlling hyperactivity and aggression in this group. Improved social integration appears to be due in part to greater self-acceptance and improvement in emotional controls, as suggested by Freed.§ The question is raised as to how chlorpromazine produces this effect.

The qualitative change in emotional control is best exemplified by the appearance of depression in some cases. The six patients becoming depressed in this group had a history of emotional deprivation of much greater severity than the other members of the group. All these six children had experienced a relatively good relationship which was lost at some time during their lives. It is not clear whether the drug produces this change in ego defenses directly or indirectly. The concept of the drug having an influence on ego integration is interesting when considered in relation to the following neurophysiological theory of action—that the reticular activating system of Magoun is possibly an area directly acted upon by the drug.‖ Jasper's work on this system indicates that it is concerned in the integration of total cortical functioning.[10]

§ Freed, H.: Treatment of Hyperkinetic Emotionally Disturbed Children with Prolonged Administration of Chlorpromazine, read before the American Psychiatric Association, Atlantic City, N. J., May 10, 1955.

‖ References 6 and 9; Freed, H.: Treatment of Hyperkinetic Emotionally Disturbed Children with Prolonged Administration of Chlorpromazine, read before the American Psychiatric Association, Atlantic City, N. J., May 10, 1955.

TABLE 6.—*Delinquent Group*

Degree of Improvement	Patients, No.	Ages, Yr.	Patients in Therapy, No.	Dose, Mg./Day
Slight.....	1	15	1	150
Mild.....	0	..	..	...
Moderate.....	2	13-15	1	150-225
Extensive.....	1	14	1	300
Inconclusive....	1	14	1	150
No change.....	1	15	1	300-600
Worse.....	3	12-15	1	75-450

DELINQUENT GROUP (TABLE 6)

For our purpose, this is a group of nine patients with behavior disorders who have come into conflict with legal authorities because of their acting out. The following history is representative of the group.

A boy, now 14 years old, was admitted to the Unit at the age of 13. He had been committed to the Division of Child Guardianship as neglected at the age of 2½. Little is known of his birth and development prior to this time. He was placed in a foster home, and his first foster mother requested his removal because of hyperactivity and soiling night and day. Since then he has been in many foster homes, and reports repeatedly emphasize fighting with other children and not trying at school. His first reported theft occurred at the age of 8 years, and by the age of 9 years reports emphasized his destructiveness. However, he had remained in one foster home for two years prior to admission to the hospital and had adjusted fairly well until he was disappointed about not getting onto the school baseball team. From this time, he went on a rampage of stealing, although the things he stole were unimportant. This was associated with much fighting and destructiveness interspersed with episodes of sullenness and depression. During the time he has been in the hospital his behavior has alternated between being extremely aggressive and hyperactive and being somewhat withdrawn and depressed.

In the evaluation of change in this delinquent group, marked improvement was found in one patient, an extremely hyperactive and violently destructive boy. At the time of medication some depression was evident; this became slowly more marked after discontinuance of the drug, and the improved behavior continued.

Moderate improvement was noted in two children who showed extensive reduction in their hyperactivity, impulsivity, and aggressiveness. On withdrawal of the drug, the depression lifted, while much of the improved behavior in other areas remained.

Slight improvement was seen in a boy showing no obvious anxiety or hyperactivity prior to medication. He was somewhat surly and irritable, but this lessened when he took chlorpromazine. Another boy had shown no aggressiveness or motor hyperactivity during the six months prior to medication. His behavior was characterized by a flood of superficial verbalizations.

The one patient exhibiting no change was a girl with a previous history of two brief paranoid schizophrenic episodes. At the time of starting the medication she manifested alternating depression with much self-mutilation and impulsive aggression directed towards herself as well as others. Chlorpromazine only controlled her behavior when she was very drowsy, and even then she would suddenly show brief episodes of extreme aggression as before. Though she might be classified in the schizophrenic group, her behavior on medication resembles that of a typical delinquent girl who became worse on the drug. This latter adolescent had shown frequent explosive rages, preceded by a period of marked overactivity, prior to medication. On medication these rages were less frequent and the hypomanic behavior of shorter duration, though each outburst was severer and difficult to control.

Two remaining patients were considered worse. One showed a swing to depression which overshadowed the reduction in his hyperactivity and persisted following cessation of medication. The other showed reactivation of previous schizoid behavior but with increased intensity.

In all patients in individual therapy the therapist commented on improved relationship with the patients and greater ease and success in working with them.

Comment.—All cases showing depression on medication had suffered great emotional deprivation during the first five years of life. This emotional deprivation was a feature significantly less prominent in the histories of those not so depressed on medication. The severer and more persistent depressions appearing during administration of the drug were in those who had showed past attempts to tolerate internal tension at any time and who had attempted solution of conflicts by acting out.

Observations of the latter group seem to substantiate the theory of the depressive nucleus of delinquency and add support to

the hypothesis of its being related dynamically to the manic-depressive disorder of adults.¶ The "acting out" is considered a defense against depression. Since chlorpromazine uncovers latent depression, it has the tendency in those patients who cannot tolerate much internal tension (depression) of increasing their overactivity and aggressivity. These depressive and hypomanic tendencies should be considered when chlorpromazine is used on an outpatient basis with delinquents.

It remains uncertain whether the immobilizing effect of the drug is of importance in intensifying the depressive and hypomanic behavior of these patients. This immobilization is not only from the tranquilizing action but also apparently from a direct effect on the motor pathways, which is shown by the production of transitory Parkinson's syndrome in some patients.

TABLE 7.—*Brain Damage Group*

Degree of Improvement	Patients, No.	Ages, Yr.	Patients in Therapy, No.	Dose, Mg./Day
Mild	3	8, 11, & 14	0	150-225
Moderate	1	10	0	150
Worse	2	7 & 13	0	150
No change	1	14	1	150

The effect of restriction of the activity of delinquents by institutionalization is known to produce depressive and neurotic features. However, the six patients here discussed had been in the hospital six months or longer prior to the study and had shown no such extreme hypomanic and depressive features prior to chlorpromazine. Therefore, it seems indicated that chlorpromazine played a role over and above that of restriction by institutionalization.

BRAIN-DAMAGE GROUP (TABLE 7)

There were seven patients who had suffered brain damage, usually severe, which accounted in the main for their behavior prior to medication. The following history typifies this group.

A girl, now 10 years old, was admitted to the hospital at the age of 3 years. Her first 9 months of life were apparently normal and uneventful. She had convulsions associated with high fever at the age of 9 months. At the age of 2 years she was hospitalized with a diagnosis of measles encephalitis, having had a number of convulsions following the development of the measles. After this illness, with its frequent convulsions, the child babbled, was unable to walk, and became restless and irritable, grabbing, tearing and destroying things within reach; previously she was able to speak and walk as well as could be expected of a 2-year-old and never was a bother. She was admitted to our hospital because of her great hyperactivity and destructiveness and her need for complete physical care. At the time of admission, the physical examination showed evidence of spastic paraplegia and the I. Q. estimated on the Binet scale was 27.

By the age of 7 years her behavior in the hospital had approached that seen at the time of medication. She needed complete care and spent much time tearing up paper or wandering around the ward rather aimlessly. Her walking was clumsy.

In this group the four children who showed improvement did so in the areas of hyperactivity, aggressiveness, and sociability, as in the cases of the behavior-disorder group. However, the change was much less marked, and the dose of chlorpromazine required to reduce hyperactivity and aggressiveness was also so high that the children slept most of the day.

One of the patients becoming worse was a boy with chronic arrested hydrocephalus and seizures, who needed an increase in phenobarbital to control his seizures. He endeavored increasingly to play with other children, which resulted in much frustration for him, leading to increased hyperactivity and assaultiveness. The other patient becoming worse was a girl with moderate cerebral palsy who had previously been described as having "an autistic element in her behavior." The history of her earlier years was not reliable, although a fairly definite change in her behavior occurred around 3 years of age. If she was considered as schizophrenic with acute onset of the psychosis at

¶ Kaufmann, I., and Makkay, E.: Juvenile Delinquency and the Manic-Depressive Disorders, read before the American Orthopsychiatric Association, Chicago, March 1, 1955.

3 years of age, she would be exhibiting the pattern of activation of infantile behavior, as was observed in some of the chronic schizophrenic patients.

Comment.—The value of chlorpromazine in these patients seems to be limited. Large doses need to be used, often resulting in the children's sleeping excessively. There appears to be a possibility of activating convulsive states. Certainly the drug was of value in reducing some of the over-activity present in these patients, despite the relative lack of success.

COMPLICATIONS

There were very few complications. Serial blood studies revealed no remarkable changes, and no jaundice was observed. The frequent occurrence of drowsiness has already been noted. There was one case with an urticarial reaction, but this disappeared in three days without specific treatment or the stopping of medication. Two cases showed mild edema of the face, and one had edema of the ankles. These patients were carefully observed, but they showed no tendency to become worse during the period of medication; the symptom disappeared after cessation of medication. Two cases with epilepsy had an increased number of seizures and required an increase in their dosage of phenobarbital. This presents a paradox because of the known potentiating effects of chlorpromazine on barbiturates and because of the experimental evidence that chlorpromazine protects animals against the epileptogenic action of pentylenetetrazol (Metrazol). The effect of chlorpromazine on seizures needs further investigation.

About 10% of the patients on higher dosage had a mild definite Parkinson syndrome, primarily manifested by the typical rigidity but also showing some tremor for brief periods. This disappeared rapidly when the drug was stopped.

SUMMARY AND CONCLUSIONS

Fifty-eight severely disturbed children were treated with chlorpromazine. Their disorders were classified in the following diagnostic categories: schizophrenia, ranging from the acute to the chronic; various behavior disorders, some showing antisocial acting out to a degree considered delinquent; extensive organic brain damage with secondary severe behavior disorder. Forty-four patients given the drug showed some degree of improvement, five were unchanged, and five became worse. In four patients the results were inconclusive.

The best results with chlorpromazine were obtained in behavior disorders, where the drug proved valuable chiefly for reducing hyperactivity and aggressiveness. Some of those patients having an underlying depression as an important aspect of the dynamics of their disturbance became overly depressed on the medication. On the other hand, some with latent depression showed increased acting out, which was considered their defense against the tension of the depression they had not the ego strength to tolerate.

The shorter the duration of the schizophrenia, the better were the results. The acute disorders responded well. The improvement in the chronically ill patients was felt to be encouraging for a condition so resistant to change. One interesting feature found in this group was the appearance of more florid schizophrenic symptoms always associated with or followed by regression and over-all improvement in the patient's ability to relate. The least successful results were obtained with those patients showing extensive brain damage.

A hypothesis for further clinical validation is that the primary action of the drug can best be described in terms of its effect on ego function: It strengthens the latent healthy functions of the ego. In connection with this, the obvious reduction of hyperactivity and aggressiveness is considered an indication of increase in ego strength. Another hypothesis is that there may be a connection between the apparent effect of the drug on ego integration and its suggested action on the reticular activating system.

REFERENCES

1. Winkelman, N. W., Jr.: Chlorpromazine in the Treatment of Neuropsychiatric Disorders, J. A. M. A. **155**:18 (May 1) 1954.

2. Kinross-Wright, V.: Chlorpromazine: A Major Advance in Psychiatric Treatment, Postgrad. Med. **16**:297 (Oct.) 1954.

3. Pollack, B.: Preliminary Report on the Effect of Thorazine in the Treatment of 248 Mental Patients in the Rochester State Hospital, Psychiat. Quart., to be published.

4. Kelley, J. W.: Thorazine-Chlorpromazine, Nebraska M. J. **39**:305-307 (July) 1954.

5. Ayd, F. J., Jr.: Treatment of Psychiatric Patients with Thorazine, South. M. J. **48**:177-186 (Feb.) 1955.

6. Lehmann, H. E., and Hanrahan, G. E.: Chlorpromazine: A New Inhibiting Agent for Psychomotor Excitement and Manic States, A. M. A. Arch. Neurol. & Psychiat. **71**:227-237 (Feb.) 1954.

7. Gatski, R. L.: Chlorpromazine in the Treatment of Emotionally Maladjusted Children, J. A. M. A. **157**:1298-1300 (April 9) 1955.

8. Goldman, D.: Treatment of Psychotic States with Chlorpromazine, J. A. M. A. **57**:1274-1278 (April 9) 1955.

9. Hiebel, G.; Bonvallet, M., and Dell, P.: Action de la chlorpromazine au niveau du système nerveux central, Semaine hôp. Paris **30**:2346-2353 (June 6) 1954.

10. Jasper, H. H., in The Biology of Mental Health and Disease: The Twenty-Seventh Annual Conference of The Milbank Memorial Fund, New York, Paul B. Hoeber, Inc., 1952.

Special Articles

THE ADVERSE EFFECTS OF EARLY INSTITUTIONALIZATION OF MENTALLY SUBNORMAL CHILDREN

MALCOLM J. FARRELL, M.D., Waverley, Mass.

IN RECENT years there has been a growing tendency among members of professional groups to advise and even urge early institutionalization of mentally subnormal children, especially the Mongoloids. The resultant pressure brought to bear on institutions for the mentally subnormal has forced those facilities to accept and provide for infants, many only a few days old. It is the purpose of this paper to point out that such advice may not only be ill advised but may even be harmful to both the parents and the child.

Every administrator of such an institution has had the experience of interviewing a distraught and frantic father whose wife has just given birth to a Mongoloid child. Too often he has been urged by the attending physician to take immediate steps toward institutionalization. He has been warned, for example, that should the child be taken home, the normal strong attachment between mother and child will make future separation, should it be necessary, a heartbreaking experience for both. The negative and hopeless sides of the picture are stressed, rather than its positive and hopeful aspects.

It is not my intention to minimize the seriousness of the advent of such a child in a family. Because of the tremendous emotional investment which both parents have in any pregnancy, it is without doubt a most serious matter to have the birth of an abnormal child. Therefore, any advice given must be carefully and thoughtfully weighed in terms of its possible effect on the parents, on the child, and on other members of the family. Caution is urged so that the advice is not given hastily or empirically.

At the last meeting of the American Association on Mental Deficiency an entire morning in the Section on Administration was devoted to this subject, and the practice of indiscriminate early admission was condemned. In the course of the discussion a director of an institution in the Middle West reported a heart-rending interview with a soldier father, who had been advised to arrange for immediate admission of his newly born Mongoloid child so that his wife could be told that the child had died. This emotionally disturbed and confused father asked, "How can I live with my wife and live with such a lie?" The kindly and somewhat outraged director spent much time reassuring the father, helping him to better understand his problem and think it out more rationally. The father finally decided that his wife should be told. When she left the hospital, the parents took the child home—a decision they made themselves.

Dr. Martha Elliot,[1] Chief of the Children's Bureau, Washington, D. C., recently told of a visit of a member of her staff to a State School. She stopped by the bed of a 2-year-old Mongoloid child with blond curly hair and a rather winning smile. The staff physician said: "That is a sad case. When the baby was born the physician told the parents they had a monster, that they should never see the child, they should tell the family and friends it had died and send it at once to an institution. Too shocked to think clearly, they followed this advice. Recently the par-

Submitted for publication Aug. 17, 1955.

Read at the 174th Annual Meeting of the Massachusetts Medical Society, Boston, May 19, 1955.

Superintendent, Walter E. Fernald State School; instructor in Psychiatry, Boston University School of Medicine and Tufts University School of Medicine.

ents visited in a home where there was a mongol, and to their surprise and dismay found the child not a monster but an accepted member of a loving family. Now they feel they abandoned their child and are bitter and resentful against the physician. The child is only moderately retarded, but two years in an institution have not given her the chance which she could have gotten from a home and loving parents."

These are no doubt extreme cases, but they do point up the need for a frank discussion of the problem by persons called upon for advice. Needless to say, the consensus among the discussants at the Section meeting was disagreement with the principle that early institutionalization should be advised in all cases.

The subject was carefully considered by an Expert Committee on the Mentally Subnormal Child of the World Health Organization.[2] Published reports of the World Health Organization represent accepted policy of that organization. It was the unanimous opinion of the Committee, of which I was a member, that:

1. Parents inevitably experience profound shock when it is discovered that they have a subnormal child. In many cases they will feel a groundless personal guilt, or perhaps, half-consciously, each will blame the other for the child's condition. In most cases, these distraught parents need the opportunity for frank discussion with a specialist in both the field of mental subnormality and of mental health. It may be necessary for many discussions, perhaps even extending over a period of years, since the parents cannot be expected to understand and face the full consequences of matters of such strong emotional significance after a single interview. They should be given accurate information, frank and full answers to their questions, advice on how best to cope with the problems of upbringing not found in normal children. They should also be helped to guard against demanding either too much or too little of the child.

2. Once a diagnosis has been arrived at, a major decision which has to be taken is whether the child can be cared for at home or should be placed in an institution or foster home. Sometimes a child can be cared for at home while very young but will need institutional care when he is older.

3. Three aspects should be carefully considered before institutional placement is recommended: (*a*) the actual condition of the child; (*b*) the mental health of the family, the competence of the mother, and the possible effect on the family of retaining a subnormal child in its midst, and (*c*) the home conditions and financial circumstances of the family.

4. Home care is recommended unless serious family problems will arise as the result of retaining the child in the home. Even severely handicapped children can be cared for at home, if parents take a realistic view of the situation and make use of available child-health service.

5. It is denied categorically that all subnormal children should be institutionalized. The decision to place a child in an institution should be based on the needs of the individual child and his family. It must be borne in mind that early institutionalization not only fails to relieve the stress but may intensify it. Early placement is likely to be interpreted by the troubled parents as a confirmation of their own guilt feelings and an irrevocable rejection of the child. Even a good institution is no substitute for the essential emotional interplay between parents and child.

In its report to the Massachusetts Legislature,[3] the Special Commission established to make an investigation and study relative to training facilities available for retarded children also felt strongly on this subject. The report states: "The mentally retarded child is, first of all, a child, and thus entitled to the same consideration as every other child. Secondly, he is a handicapped child and as such is entitled, with all handicapped children, to every aid we can give him to function, within his handicap, as a child."

Certainly a most important factor in a child's emotional and intellectual development is the interpersonal relationship between parents and child.

A number of experts interested in this area, working independently and in several different countries, concur on the validity of this thesis. In this connection reference may be made to the work of John Bowlby, Director of Child Guidance, Department of the Tavistock Clinic [4]; Harold Skeels, N. I. M. H., U. S. Department of Public Health, and his various collaborators [5]; Lauretta Bender, Psychiatric Division, Bellevue Hospital [6]; Arnold Gesell and Catherine Amatruda, Yale University,[7] and K. Roudinesco and G. Appel,* who are currently investigating this problem in Paris. As Bowlby states in his critical discussion of literature available on this subject, "Direct studies are the most numerous. They make it plain that, when deprived of maternal care, the child's development is almost always retarded—physically, intellectually, and socially." Of equal pertinence to the problem under consideration is the report of the Committee on the Family of the Group for the Advancement of Psychiatry [8] which states that, "from the point of view of the individual it is the family that determines . . . what he calls 'home' with all the implications for the sense of personal identity that local, regional and national sentiments contribute. . . . It is in the family transactions that . . . ascribed roles are initially learned. . . . In residential institutions for children . . . the parental roles are strung out among a wide variety of parent substitutes . . . no one really 'belongs to anybody.'" The report concedes that the purely biological needs of the child during his period of dependency can be met to a fairly adequate degree by agencies other than the family unit, but the Committee is of the opinion that "more important, perhaps, is the child's need for love, approval and security. This latter need can tentatively be further specified as the need for a consistent pattern of rewards and punishments in the context of a basic emotional acceptance and understanding of the child by its parents."

The Commission report continues,

> It is for every child that we crave security—not only for the hale and hearty, the capable ones, and those of stable personality. The challenge is even greater for those who must be helped to become hale and hearty, capable and stable; or, failing that, to function at least to the limits of their possibilities. This is the right of all children. It is also the duty of society, since whatever profits, the children will ultimately redound to the good of the community.

The Conclusion of the Commission is pertinent to this paper. It states:

> If we conclude that the fabric of our democratic way of life shall have for its pattern the education of all the children of all the people, cognizance must be taken of the individual differences which are the fibers of its very being. If we neglect to benefit the individual child to his fullest capacity, then we are depriving him of his inherent birthright—the opportunity for greatest self-realization. Failure to provide the maximum in educational opportunity for the mentally handicapped in this scientific age is to withhold from them the very powers of self-preservation, and to sin against posterity by failing to train for the future all who are to become members of its social group.

The same may be said for emotional deprivation.

Professional workers in institutions for the mentally subnormal often witness the distressing experience of a mother who, for the first time, sees her Mongoloid child. Often this meeting is a few years after the birth of the child. In such instances, the parents had been advised not to take the child home from the maternity hospital for a variety of reasons, including the possibility that the parents would become overattached to the child. However, the parents, especially the mother, did not forget the child. She wondered how it looked, how it behaved, and she had all the thoughts common to all mothers. Finally the time arrived when she just had to see the child, and what she saw was not the horrible monster she had been led to expect but a lovable child ready to return parental affection. The emotional reaction of the parent to this discovery is often terrific and could become pathological.

* Cited by Bowlby, J.[4]

Much has been done to ease the burden of retaining such a child in the family setting. In most instances only ordinary pediatric care is necessary. When the time for education and training arrives, Massachusetts [9] and some other states have provided subspecial classes for those who cannot attend the traditional special classes. The Special Commission has been continued and is now studying the possibilities of providing sheltered workshops for the handicapped person who has finished his formal education and training. In short, many facilities either have been provided, or are being planned, to make it possible for these handicapped people to remain at home. Even in places where such opportunities are not yet available, there are numerous instances of such persons making a satisfactory adjustment in the community, where they are accepted by their families and neighbors. In a large measure, the adjustment of these children and the attitudes of siblings depend on the emotional reactions of the parents and their ability to resolve their inevitable guilt feelings and disappointments.

It is recognized that at some time institutionalization may be necessary. If such need occurs, the retarded child who has had the advantages of family and community acceptance will find adjustment to the institution easier because of appropriate education and training, especially in the realm of living with others.

SUMMARY

Attention has been invited to the serious and far-reaching implications of indiscriminate and universal advice of early institutionalization of mentally subnormal children. Such decision and advice should be made on an individual basis, taking into account the many factors governing the emotional needs of the child, the parents, and other members of the family group.

It is the right of parents to assume the responsibility of deciding the future course for their child. It is the duty of the physician to guide them through the many ramifications of the problem in arriving at a decision.

REFERENCES

1. Eliot, M. M.: How the Children's Bureau Helps Retarded Children, presented at Meeting of National Association for Retarded Children, Boston, Oct. 23, 1954.

2. Report of a Joint Expert Committee Convened by the World Health Organization with the Participation of United Nations, ILO and UNESCO: The Mentally Subnormal Child, WHO Technical Report, Series No. 75, April, 1954.

3. Report of the Special Commission Established to Make an Investigation and Study Relative to Training Facilities Available for Retarded Children, State House, Boston, December, 1953.

4. Bowlby, J.: Maternal Care and Mental Health, World Health Organization Monograph Series No. 2, 1952.

5. Skeels, H. M., and Dye, H. B.: A Study of the Effects of Differential Stimulation on Mentally Retarded Children, Am. J. Ment. Deficiency **44**: 114-136 (June) 1938.

6. Bender, L.: Psychopathic Behavior Disorders in Children, in Handbook of Correctional Psychology, edited by R. M. Linder and R. V. Seliger, New York, Philosophical Library, Inc., 1947, pp. 360-377.

7. Gesell, A., and Amatruda, C. S.: Developmental Diagnosis: Normal and Abnormal Child Development, Ed. 2, New York, Paul B. Hoeber, Inc., 1947, pp. 280-291.

8. Report No. 27: Integration and Conflict in Family Behavior, Group for the Advancement of Psychiatry, Committee on the Family, August, 1954.

9. Chapter 514, Acts of 1954, Massachusetts Legislature.

Case Reports

GENERALIZED XANTHOMATOSIS WITH CALCIFIED ADRENALS

A. ABRAMOV, M.D.
S. SCHORR, M.D.
and
M. WOLMAN, M.D., Jerusalem

THIS REPORT deals with a case of generalized xanthomatosis which exhibited an unusual feature—massive calcification of the adrenals. Massive bilateral calcification of the adrenal glands in early infancy is a very rare finding, and very few cases have been reported in which this lesion has been discovered on the plain x-ray picture in vivo.

REPORT OF CASE

A 2-month-old girl was admitted to the pediatric department of the Hadassah University Hospital on March 12, 1954, from another hospital, with the diagnosis of suspected acute abdomen. The infant had been healthy and had gained weight satisfactorily on breast feeding until a week before admission, when she started to vomit, although not forcefully. On admission the infant appeared very ill and had a pale yellowish complexion, but no abnormal pigmentation of the skin was noted. The breathing was superficial. The abdomen was distended, and no peristaltic waves were heard. The liver was palpable for 4 to 5 cm. below the costal margin. The spleen was enlarged and palpable for about 3 cm. below the costal margin. There was slight pitting edema of both legs.

Laboratory Findings.—Urine, normal. Blood cell count: RBC, 2,600,000 cu/mm. Hemoglobin, 6.5 gm/100 cc.; WBC, 7200; reticulocytes, 1.4%; thrombocytes, 73,000. Blood urea, 18 mg/100 cc. CO_2-combining power, 30 vol. %. Na, 280 mg/100 cc. K, 23 mg/100 cc. Cholesterol, 166 mg/100 cc. Total protein, 4.5 gm. Albumin, 2.7 gm. Globulin, 1.8 gm. Bilirubin, 6.8 mg/100 cc. Bile pigment (Meulengracht), 100 units. Bilirubin (Van den Bergh): direct-reacting, +; indirect-reacting, +++. Thymol turbidity, 2.9 units. Cephalin +.

Received for publication Sept. 8, 1955.

From the Departments of Pediatrics, Diagnostic Roentgenology, and Pathology of the Hadassah University Hospital.

X-Ray Examination.—While x-ray films of the barium-filled gastrointestinal tract (done in the other hospital) were being interpreted, two symmetrical triangular massively calcified shadows were observed at the two sides of the first and second lumbar vertebrae. In the anteroposterior and lateral plain films done 24 hours after the previous examination, the intestinal loops were still filled with barium. The calcified opacities were found to be situated above the upper pole of each kidney and were interpreted as calcifications of the adrenal glands (Figs. 1 and 2).

Fig. 1.—Anteroposterior x-ray of abdomen. There are massive calcifications of triangular shape in both adrenals.

Treatment.—A stomach tube was introduced, and a large amount of yellowish fluid was removed. Fluids and blood were administered intravenously. Penicillin and streptomycin were also given. On the second day of hospitalization cortisone and adrenal extract (Supracort) were given. On the third day of hospitalization the condition deteriorated and the patient died.

Autopsy.—Autopsy was performed two hours after death. The pertinent gross findings were as

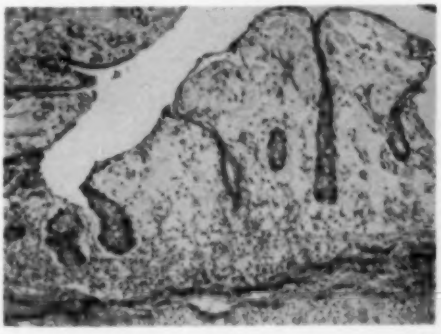
Fig. 2.—Lateral x-ray of abdomen. The massive calcifications are situated near the vertebral column.

Fig. 3.—X-ray film of the postmortem specimens of the right kidney and adrenal gland. Note a thin margin of uncalcified adrenal cortex.

follows: In the abdomen there was about 80 cc. of turbid golden-yellowish fluid. The intestines were dilated and appeared of a similar color, with a swollen mucosa exhibiting thick soft folds. The mesenteric lymph nodes were large, orange-yellow, firm, and elastic. Their cut surfaces were moist and yellowish and appeared homogeneous. Lymph nodes elsewhere in the body were enlarged and of similar appearance. The liver weighed 325 gm.; it was firm and of a yellow color similar to that of honey. Cut surfaces were less firm than usual and dull. The yellow tone was general, but it appeared more intense at the periphery of the hepatic lobules. The spleen weighed 125 gm. Its capsule was tense and in parts thickened. The consistency was firm and fleshy. Cut surfaces were meat-red, did not contain any visible follicles, and appeared homogeneous. The adrenals were large and weighed together 15 gm. Their consistency was hard, and they were difficult to cut. Cut surfaces revealed a wide cortex of a yellowish-white color; the external 1 to 2 mm. of the cortex was similar in appearance to the lymph nodes, while more medially the tissue was white, hard, and brittle. No medulla could be distinguished within the whitish hard central core of the glands (Fig. 3). Yellowish-gray areas of consolidation were found in the lower lobes of both lungs. The bone marrow of the ribs and vertebrae was of a grayish hue. The thymus weighed 5 gm., and its color and consistency were similar to those of the lymph nodes. No noteworthy changes were encountered in the brain, heart, kidneys, or other organs.

Microscopical Examination: The following is a description of the microscopic changes as studied by routine histological methods such as hematoxylin and eosin, Mallory's azan, and van Gieson's stains.

Fig. 4.—Ileum. Swollen and low villi. The lamina propria is full of xanthomatous cells. Hematoxylin and eosin; reduced from mag. × 120.



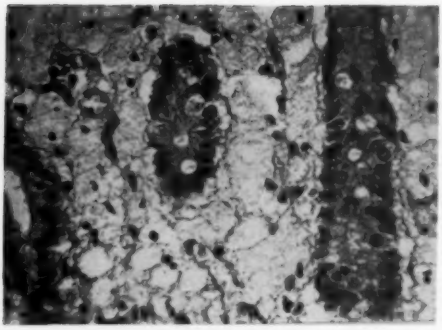


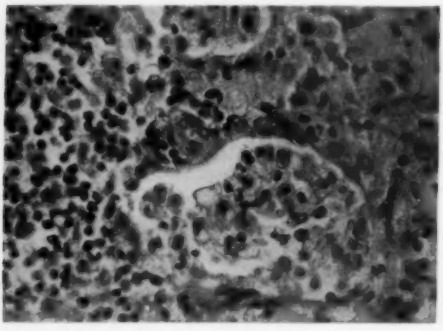
Fig. 5.—Ileum. The lamina propria mucosae is full of xanthomatous cells. In some cells the vacuoles have coalesced to form large fat globules. Hematoxylin and eosin; reduced from mag. × 400.

Results of special studies made with the aid of histochemical methods are described in the following paragraph.

In the lungs there were foci of bronchopneumonia which were remarkably rich in foamy histiocytes. In the intestine the mucosal lamina propria was full of large foam cells. The villi, laden with foam cells, were swollen and low (Fig. 4). The cells were large, up to about 30μ in diameter, with central or peripheral small compact nuclei. The cytoplasm appeared in some cells finely vacuolated; in other cells the vacuoles appeared to have coalesced. The vacuoles, whether small or large, had clear-cut margins; the smaller ones gave the cells a foamy, net-like appearance (Fig. 5).

All lymph nodes examined had different amounts of similar cells. The lymphatic follicles were small in some nodes and appeared compressed by sinuses which were lined with such cells (Fig. 6). A similar change was found in some areas of the thymus (Fig. 7).

Fig. 6.—Lymph node. Xanthomatous change of intersinusoidal reticulum cells, some sinus-lining cells, and presence of xanthomatous cells within the sinuses. Van Gieson stain; reduced from mag. × 370.



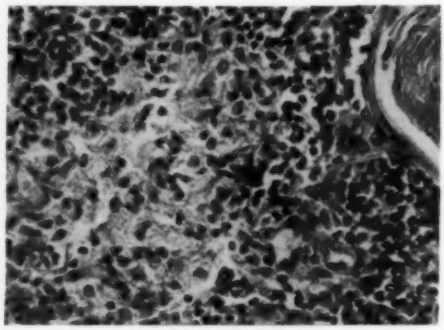


Fig. 7.—Thymus. Xanthomatous change encroaching on the lymphatic tissue. Van Gieson stain; reduced from mag. × 360.

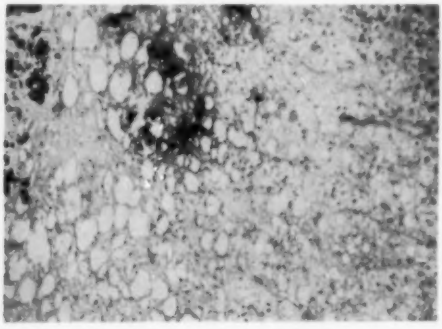
In the liver the normal architecture was hardly recognizable. The lobules were of different sizes and were separated by bands of connective tissue. The liver cells at the periphery of the lobules contained many fat droplets. In the connective-tissue bands there was a moderate bile-duct proliferation.

In the lumbar vertebrae and in the ribs examined, the bone marrow was hyperplastic. Here and there small collections of histiocytes similar to those described above were found.

The spleen contained small and ill-delimited follicles. The red pulp appeared hyperplastic and contained hypertrophic reticulum cells and sinus endothelium cells. In a few of these cells some, not very conspicuous, fat vacuoles were observed. The pulp contained many active hemopoietic foci.

In the adrenals only the glomerulosa and, in places, a part of the fasciculata were preserved and appeared normal. The inner part of the cortex was found replaced by foam cells, empty spaces corresponding in form to fat globules and cholesterol

Fig. 8.—Adrenal. Normal cortical tissue on the extreme right is replaced (towards the left) first by xanthomatous tissue, then by frank adipose tissue and areas of calcification (in the center and on the left side). Hematoxylin and eosin; reduced from mag. × 105.



crystals, and amorphous partly calcified masses (Fig. 8). No noteworthy changes were observed in the brain, eye, skin, heart, larynx, parotid, thyroid, pancreas, kidneys, uterus, Fallopian tubes, ovaries, and bladder.

Histochemical Study of the Foam Cells: The foam cells found in the different organs were studied by the use of certain histochemical methods.

It was found that the lipid contained within the foam cells of the intestine, lymph nodes, and thymus, as well as that found in the adrenals, gave identical reactions. It stained with Sudan IV; most of it was doubly refractile; it was not stained by the periodic acid-Schiff technique; it was soluble in cold absolute alcohol, and it gave a positive Liebermann-Burchardt reaction. Furthermore, the lipid was not stained by the Weigert type of methods used for demonstrating myelin (hematoxylin and like methods). In a small minority of the foam cells in lymph nodes there were droplets which were stained by the periodic acid-Schiff technique.

In the spleen the lipid of the few foam cells reacted in the same manner. In the liver, on the other hand, most of the lipid was not doubly refractile and did not give a positive Liebermann-Burchardt reaction.

COMMENT

The autopsy findings and the results of the histochemical investigation indicate that the case is one of generalized xanthomatosis. The positive Liebermann-Burchardt reaction, the stainability with Sudan, and the double refractivity, as well as the solubility characteristics and the absence of staining by the periodic acid-Schiff technique show that the lipid contained within the cells is predominantly cholesterol.

The cholesterol level in the blood indicates that the case is normocholestreolemic. Furthermore, the lack of inflammatory reaction in any one of the organs affected shows that the xanthomatous process is systemic and primary in this case.

The distribution of the lesions is noteworthy. The organs which were affected most intensely were the intestines and the adrenals. While the involvement of the lymph nodes, vertebrae, and thymus is common in this disease, the sparse involvement of the spleen and liver is also unusual.

The most remarkable feature of this case is the widespread calcification in both adrenals. Massive adrenal calcification found early in life presents a problem of a differential diagnosis. In early infancy mainly two conditions have to be suspected and differentiated: (1) adrenal hemorrhage, or suprarenal apoplexy; (2) generalized xanthomatosis. Hemorrhage into the adrenal gland followed by calcification has been found at autopsy in an infant only eight days old by Snelling and Erb (1935). Drucker and Rodriguez (1955) reported a case of a 4-month-old infant with extensive bilateral calcified adrenals who lived for almost two years after the initial extensive hemorrhage. On the other hand, calcification of the adrenals should also raise the suspicion of a systemic disease, such as generalized xanthomatosis.

Alexander (1946) reported the occurrence of bilateral adrenal calcification in a 6-week-old boy with Niemann-Pick's disease. The adrenal calcification was visualized radiographically and confirmed by postmortem examination.

Caffey (1950) reported a case of bilateral calcified adrenals in which the necropsy findings corresponded to a reticulosis of the Niemann-Pick type. No attempt was made to confirm the diagnosis by chemical or histochemical studies. In a personal communication, Caffey has reported a similar case, which was seen at the University Clinic of Cleveland.

The x-ray differential diagnosis should also include consideration of tuberculosis, associated with Addison's disease, as well as neoplasms such as neuroblastoma, ganglioneuroma, and carcinoma of the adrenal glands associated with several deposits of calcified material. The calcified areas in these conditions are much smaller and less widespread.

The histological appearance of the adrenals leaves no doubt as to the pathogenetic importance of the xanthomatous change for the calcification. Although the exact mechanism of this calcification cannot be determined, the presence of calcification in similar pathologic processes allows the formulation of some possibilities. Some German authors (cf. Andreas, 1949) have described a new

disease entity, "lipocalcinogranulomatosis," which represents xanthomatosis associated with necrosis of the affected cells and calcification. An association between cholesterol deposition, necrosis, and calcification is common in a number of disease processes, e. g., atheromatosis and hemorrhages. It is possible that the calcium deposition in this case was due to saponification by calcium of fatty acids released by hydrolysis of cholesterol esters.

SUMMARY

A case of generalized normocholesterolemic xanthomatosis in a 2-month-old infant is described, in which massive calcification in the adrenals was diagnosed roentgenologically during life. The distribution of the lesions was unusual, as the small intestine, lymph nodes, adrenals, and thymus were affected most intensely.

BIBLIOGRAPHY

Alexander, W. S.: Niemann-Pick Disease: Report of a Case Showing Calcification in the Adrenal Gland, New Zealand M. J. **45**:43, 1946.

Andreas, E.: Die Lipocalcinogranulomatosis—eine neue Lipoidose, Med. Klin. **44**:913-916, 1949.

Caffey, J.: Pediatric X-Ray Diagnosis, Ed. 2, Chicago, The Yearbook Publishers, Inc., 1950, p. 527.

Drucker, V., and Rodriguez, C. E.: Extensive Bilateral Calcification Within Adrenal Hemorrhage, Radiology **64**:258-261, 1955.

Snelling, C. E., and Erb, I. H.: Hemorrhage and Subsequent Calcification of the Suprarenal, J. Pediat. **6**:22-41, 1935.

News and Comment

ANNOUNCEMENTS

Convention of The Intermountain Pediatric Society.—The Intermountain Pediatric Society will hold its annual convention in Sun Valley, Idaho, June 7, 8, 9, 1956. Guest speakers will include Dr. Douglas N. Buchanan, Chicago; Dr. Amos U. Christie, Nashville, Tenn.; Dr. Wm. L. Hewitt, Los Angeles; Dr. Horace L. Hodes, New York, and Dr. Edith L. Potter, Chicago. The meeting is open to all physicians.

Course in Pediatric Oncology.—The pediatric department of Memorial Center for Cancer and Allied Diseases announces that the annual comprehensive three-day course in pediatric oncology for pediatricians, general practitioners, and health officers will be held April 25, 26, and 27, 1956. The purpose of this course is to review current concepts regarding the neoplastic diseases of children, particularly as to diagnosis, differential diagnosis, and management, and to indicate the importance of the clinician's role in the control of cancer in childhood.

Case demonstrations, clinics, and lectures will be given by the following services: Gastric and Mixed Tumor, Bone, Thoracic, Radiology, Pediatrics, Chemotherapy, Gynecology, Head and Neck, Genito-Urinary, and Neurosurgical. The faculty will consist of 20 members of the attending staffs of Memorial Hospital and Sloan-Kettering Institute for Cancer Research. The class will meet at 8:30 a. m. to 4 p. m. at Children's Pavilion, Memorial Center. The fee is $35. The class will be limited to 15 physicians.

For information address: Director, Pediatric Service, Memorial Center, 444 E. 68th St., New York.

INVAGINATION OF THE LEFT AURICULAR APPENDAGE, RESULTING IN SUDDEN DEATH

WILLIAM deG. HAYDEN, M.D.
CARL J. CRAMM, M.D.
B. H. WILLIAMS, M.D.
and
JAMES C. STINSON, M.D., Temple, Texas

THE CASE presented is one of invagination of the left auricular appendage into the left atrium, discovered at the postmortem examination of an infant 5 months of age who died suddenly after an uneventful recovery from a gastroenteritis. So far as can be determined, such an occurrence has not been reported in the literature.

A 5-month-old infant Latin-American girl was admitted to the hospital with a two-week history of diarrhea which had progressed slowly in severity and subsequently was complicated by severe vomiting. The parents had observed considerable loss of weight. Physical examination revealed a markedly dehydrated infant with a temperature of 99.6 F rectally but showed nothing else of significance. The weight of the child when nude was 8 lb. 4 oz. The family history and the past history were not remarkable. Initial study of peripheral blood showed 12 gm. of hemoglobin (80%); 4,300,000 erythrocytes, and 8400 leucocytes, with a differential count of 57% neutrophiles, 36% lymphocytes, 6% monocytes, and 1% basophiles. A diagnosis of acute gastroenteritis was made. Parenteral fluids were administered immediately. Antibiotics were given, and a formula of half-strength skimmed milk was offered. The oral eosin-methylene blue culture grew Aerobacter aerogenes; the rectal eosin-methylene blue culture grew A. aerogenes and Escherichia coli. Within 24 hours the vomiting had ceased, and the child was afebrile. At the end of 36 hours the frequency of the stools had diminished and the consistency of the stools had increased. The infant's progress was favorable, and at the end of five days strained foods were being tolerated. The blood

Fig. 1.—Heart, superior aspect. The auricular appendage is shown protruding into the left ventricle.

studies showed 12 gm. of hemoglobin (80%); 4,910,000 erythrocytes, and 9050 leucocytes, with a differential count of 60% neutrophiles, 39% lymphocytes, and 1% monocytes. On the seventh hospital day the child was seen at 7:50 a. m. Her weight was 10 lb. 3 oz., and her condition had improved to the extent that dismissal was advised for the next morning. Approximately 15 minutes later the child was discovered lifeless in bed, having received no medication or feedings in the interim.

At autopsy, the mediastinal contents were found to lie in their proper relationships. No structures were found to be exerting unusual pressure against any portion of the heart. The heart was not enlarged. The left auricular appendage, however, was found to be invaginated into the left atrium, the tip of the appendage resting in a depression made by the converging leaflets of the mitral valve. The endocardial surface of the appendage presented the usual trabeculated appearance of the pectinate musculature, and no tissue could be found connecting any portion of the appendage with either the mitral valve or any portion of the wall of the atrium or

Submitted for publication Oct. 11, 1956.

From the Department of Surgical Pathology and Pathologic Anatomy and the Department of Pediatrics, Scott and White Clinic and Scott and White Memorial Hospitals.

Fig. 2.—Heart, with left ventricle opened. Invaginated auricular appendage in left atrium. Note proximity to mitral valve.

Fig. 3.—Heart. Longitudinal section of invaginated left auricular appendage and left ventricle.

the ventricle. The appendage occupied almost the entire space of the atrium. Attempts were made to reduce the invagination manually, but the structure could not be returned to the normal position. At the same time, efforts were made to invaginate the right auricular appendage into the atrium; but the condition could not be duplicated. Later, the appendage was cut lengthwise and sections of it studied microscopically. No unusual fibrous structure or growth could be demonstrated, and there was minimal inflammation.

It seems probable that sudden death was due to obstruction to the flow of blood into the ventricle and possibly to interference with the function of the mitral valve. Whether this invagination existed at birth or developed suddenly cannot be determined. The difficulty of explaining such an anomaly on the basis of hemodynamic or extrinsic pressure relationships suggests a developmental anomaly. If the anomaly had been present from birth, it is likely that a murmur, due to the passage of blood through a small opening under increased pressure, would have been detected. No murmur was heard, and the child had not experienced attacks of syncope that might have been expected from a partial or intermittent obstruction to the flow of blood through and from the heart.

No other abnormalities were found at the examination.

SUMMARY

A case of invagination of the left auricular appendage into the left atrium has been presented. This condition probably resulted in the sudden death of an otherwise normal infant.

Obituaries

JULIUS HAYES HESS, M.D.
1876-1955

Julius Hayes Hess was born in Ottawa, Ill., Jan. 26, 1876. He graduated from Northwestern University Medical School in 1899. His internship was served at Alexian Brothers' Hospital, in Chicago, from 1899 to 1900. Apparently at this time he became interested in the care of infants and children. He then took postgraduate work at the Johns Hopkins University Hospital, in 1900, and also in hospitals in Germany and Austria in 1900-1901, 1910, 1913, 1927, 1932, and 1937.

He returned to Chicago and opened an office on the "South side" in October, of 1901. He joined the staff of the Englewood Hospital in 1901, as pathologist, and later became an attending pediatrician.

On April 15, 1902, Dr. Hess returned to Ottawa, Ill., to marry his boyhood sweetheart, Clara E. Merrifield. Their marriage was blessed by two daughters, Jean and Carol.

Returning to Chicago and his practice, not only was Dr. Hess interested in the welfare of his patients but he began to take an active part in all things medical as well as in civic affairs. He had boundless energy and liked people. No other physician in Chicago gave more time to the medical problems of the community. He taught medical students from the time he began practice. He was a good teacher and was beloved by his students. He was kindly in the advice and help he gave to many of them.

Dr. Hess served as an instructor at Rush Medical College from 1902 to 1908, and at Northwestern University Medical School from 1908 to 1913. In 1913 he joined the faculty of the University of Illinois, where he became Professor of Pediatrics, serving as Head of the Department from 1914 to his retirement in 1944. He was a member of many professional societies, among which were the American Medical Association, the American Pediatric Society and the American Academy of Pediatrics.

Although Dr. Hess was always interested in the nutritional aspects of infancy, it was by a fortuitous circumstance that he became exposed to the possibility of an incubator for prematures. A Frenchman, Dr. Martin Couney, had invented an incubator and brought it as an exhibit to Chicago's White City, an amusement park, about 1905. He claimed it could be helpful in the case of the premature infant. Dr. Isaac Abt interested his young colleague, Dr. Hess, in this device. Soon he had constructed a portable incubator which he put to the test. In 1922 he opened the premature nursery at Michael Reese Hospital with these incubators. The development and supervision of this nursery with his studies and research on prematures were to be his main medical interest and his greatest contribution to pediatrics.

Besides many contributions to medical journals, Dr. Hess was the author of five books dealing with infants and children.

Dr. Hess entered the Army in 1917 and served as a Major.

Besides many testimonials and honors bestowed upon Dr. Hess, he received the 1952 Borden Award through the American Academy of Pediatrics, which signalized his many productive contributions to the care and management of the prematurely born infant.

Dr. Julius H. Hess died on Nov. 2, 1955. He is survived by his wife and two daughters, Jean Hess Spencer and Carol Hess Saphir.

Abstracts from Current Literature

Biochemistry; Bacteriology and Pathology

TERATOGENIC ACTION OF 6-MERCAPTOPURIN. C. ZUNIN and C. BORRONE, Minerva pediat. **7**:66 (Jan. 27) 1955.

The chemical 6-mercaptipurin is similar structurally to adenine and to hypoxanthine, an SH replacing the NH and OH radicles, respectively. This chemical has been found to have a teratogenic, or tumor-producing, action. Mice in the early stages of pregnancy were given this drug in various doses. The fetuses of these animals showed such defects as retarded growth, anophthalmia, microphthalmia, hydrocephalus, and perioral hemorrhages.

HIGGINS, Boston.

THE GROWTH OF LACTOBACILLUS BIFIDUS IN HEATED AND DIGESTED HUMAN BREAST MILK. W. MARGET and G. NABER, Monatsschr. Kinderh. **103**:181-184 (March) 1955.

Of 26 different strains of Lactobacillus bifidus only 12 grew in digested (by means of added pancreatic ferment) human breast milk heated for 10 minutes at temperatures of 60 C and above. Heating above 60 C for 10 minutes inhibited growth of 14 strains of L. bifidus.

It was suggested to subdivide this organism into two types on the basis of these observations.

HARTENSTEIN, Syracuse, N. Y.

Metabolism; Infant Feeding; Milk and Other Foods

ON THE PATHOGENESIS OF CHRONIC CONSTIPATION IN INFANTS AND ITS RELIEF BY THE USE OF ADSORBING FOODS. P. NICOLAJ, Clin. pediat. **36**:872 (Nov.) 1954.

The giving of mashed squash or carrots is recommended for the relief of chronic constipation in babies.

HIGGINS, Boston.

TESTS ON THE FEEDING OF AMINO ACIDS TO DYSTROPHIC INFANTS. P. BRUSA and V. QUINTÉ, Minerva pediat. **7**:209 (Feb. 24) 1955.

Five normal and ten dystrophic infants were given Nesmida by mouth (a hydrolyzed preparation of casein and fibrin) equivalent to a 0.5% to 1% of and in addition to the regular feeding. The feedings were well taken and tolerated. An increase in the amino acid content of the blood serum with no change in the amino acid excretion in the urine indicated that the amino acids were being utilized.

HIGGINS, Boston.

THE EFFECT OF AMINO ACIDS ON THE SERUM PROTEIN PICTURE IN DYSTROPHIC INFANTS. P. BRUSA and V. QUINTÉ, Minerva pediat. **7**:281 (March 10) 1955.

The addition of amino acids, as Nesmida (hydrolyzed casein and fibrin), to the formulae of dystrophic infants resulted in the serum protein content of dystrophic infants approaching that of normal infants. In about one-half of the dystrophic infants, the γ-globulin percentage of the serum proteins was increased after this addition of amino acids to the formulas.

HIGGINS, Boston.

THE USE OF FATTY EMULSIONS INTRAVENOUSLY IN THE TREATMENT OF SEVERE DYSTROPHIES IN INFANCY. R. RAMOS, TORRES MARTY, W. OPPENHEIMER, A. M. VILA CORO, J. MIRANDA, and J. M. FRANCES, Arch. pediat., Barcelona **5**:265-284 (Nov.-Dec.) 1954.

The authors report the use of the fatty emulsion previously described in this periodical and give detailed results in the cases of four severely malnourished children. They feel that the number of cases in which it has been used are too few to draw any conclusions. The four children thus treated recovered rapidly. They feel that laboratory results show that this method is more rapidly effective than others in at least two ways: (1) rapid relief in hypoproteinemia and (2) correcting the serum globulin ratios.

Acidosis is relieved, and this method supplies needed Calories, allowing the amino acids to take their proper role in metabolism.

Other treatment, such as vitamins and antibiotics, is employed as indicated.

Dosage is 10 cc. per kilogram of body weight in infants and 5 cc. in older children. Infusion rate is slow, with a maximum of 20 drops per minute. It may be given daily or on alternate days and is always given in the fasting state.

ALLEN, Santa Fe, N. Mex.

CONDITION AND CONSTITUTION IN THE DETERMINATION OF DYSTROPHIES. ANDRES OLIVE BADOSA, Acta pediat. españ. **12**:440-448 (May) 1954.

The author uses the term "dystrophy," as indeed do all Spanish periodicals, to describe children with poor health, whether from nutritional or other environmental conditions or from the hereditary endowment of the children. Such terms as cachexia, marasmus, or athrepsia are only the severest forms of the condition called dystrophy.

The author then names factors considered constitutional, such as the structure and morphology of organs, the functioning of these, the endocrine and humoral endowment, and the biochemical reactions possible.

The conditions or environmental factors include diet, infections encountered, and any occurrence which by interaction with already present hereditary defects will plunge the child into serious illness.

The author discusses the various diatheses, constitutional hydrolability, and the puzzling failure of some infants to react to the therapy and nutritional regimens which bring most children to quick recovery.

ALLEN, Santa Fe, N. Mex.

OBSERVATIONS ON THE USE OF ARTIFICIAL HIBERNATION (HYPOTHERMIC THERAPY) IN EUROPEAN CLINICS. SANTIAGO PERDOMO ESCOBAR, Acta pediát. españ. **12**:1121-1132 (Dec.) 1954.

Dr. Escobar describes his impressions of the use of artificial hibernation in the clinics of Europe. The author is from Bogota.

He reviews the reasons for blocking peripheral nerves in an effort to prevent shock resulting from stress. He gives the composition of the various "lytic cocktails" used in producing the lowered metabolic state known as hibernation.

The drugs used are inhibitors of acetylcholine, epinephrine, and histamine. Phenergan, Largatil (chlorpromazine), and similar drugs are used in the three types of cocktails.

The details for using the cocktails with or without ice are described, and several cases discussed. The dangers of this type of treatment are discussed, and the drugs to be used in cases of emergency are atropine, to be followed by a mixture of acetylcholine, histamine, and epinephrine in proper dosages.

The author remarks that this form of treatment is much more popular in Europe than in America but ends with the statement that if in spite of antibiotics should he note a child's temperature continuing to rise alarmingly he would be likely to try artificial hibernation.

ALLEN, Santa Fe, N. Mex.

PRESERVATION OF HUMAN MILK BY FREEZING AND DRYING. U. KÖTTGEN, E. BRAUN, and V. FRIEDBERG, Deutsche med. Wchnschr. **80**:923 (June 17) 1955.

Lyophilized human milk on redissolving gave about the same electrophoretic pattern of its proteins as fresh human milk.

AMBERG, Rochester, Minn.

PENICILLIN AND VITAMIN D_2 IN YOUNG RACHITIC RATS. E. REKLING, N. F. GJEDDEBAEK, and E. STØRLING, Nord. med. **51**:300 (Feb. 25) 1954.

Oral administration of sodium penicillin G increases the action of vitamin D_2 in young rats fed on rickets-producing diet. The reason for this effect is not known.

WALLGREN, Stockholm.

STEATORRHEA IN INFECTIOUS MONOUCLEOSIS. ARNE FOSS ABRAHAMSEN, Nord. med. **51**:679 (May 13) 1954.

A baby boy 14 months old fell ill with signs of acute infection combined with mononucleosis (white blood cells 8100 with 79% mononuclear cells and typical Kinley cells). Twelve days after the beginning of the disease he displayed a steatorrhea that lasted for a little more than one week. The child was discharged healthy. The author believes that the steatorrhea was due to inflammatory lesions of the mesenteric glands.

WALLGREN, Stockholm.

THE SERUM B_{12} CONCENTRATION IN FULL-TERM AND PREMATURE INFANTS. ANDREAS KILLANDER and BO VAHLQUIST, Nord. med. **51**:777 (June 3) 1954.

This series comprises 12 full-term and 12 premature infants. In 11 cases blood was taken simultaneously from the umbilical cord and from the mother at delivery. The values obtained fell within normal adult range in all cases except two, which showed significantly higher values for which no explanation could be given. There was no difference between full-term and premature infants. There was no correlation between vitamin B_{12} and hemoglobin concentrations. The vitamin B_{12} content in the blood from the umbilical cord showed in all cases higher values than the corresponding maternal values. The method used was a microbiological one made by means of Euglena gracilis var. bacillaris.

WALLGREN, Stockholm.

MOTHER'S MILK AND BREAST-FEEDING ABILITY. ALFRED SUNDAL, Nord. med. **52**:1577 (Nov. 11) 1954.

A brief survey is presented of the composition of human milk in relation to cow's milk and the advantages of feeding with mother's milk. An investigation at the infant welfare unit of the children's clinic, Bergen, shows that the ability of mothers to breast-feed their babies was poorer in 1953 than it was 13 years ago in Oslo. The principal factors which seem to govern the breast-feeding ability are outlined, and attention is drawn to the measures of practical importance that should be taken by pediatricians, general practitioners, and the welfare centers for the purposes of increasing feeding with mother's milk.

WALLGREN, Stockholm.

THE INCIDENCE OF BREAST-FEEDING IN HELSINKI IN RECENT YEARS. HEIKKI KALLIALA, NIILO HALLMAN, and LEENA TUUTERI, Nord. med. **52**:1579 (Nov. 11) 1954.

The total number of children born in Helsinki in 1952 was 6353, of which 75% were supervised by the infant welfare centers. The percentage of infants fed with breast milk was less than 40% at the age of 3 months, less than 15% at the age of 6 months, and only 9% at the age of 9 months. There was an evident decrease of the incidence of breast-feeding in comparison to previous investigations. The period of breast-feeding was slightly longer among mothers of a higher social standing than among those living in very poor conditions. The main cause of early weaning was mastitis in 8.6%, in 9.6% some other illness of the mother, in 2.2% debility or illness of the infant, and in 9.9% the mother's work outside the home. In the rest of the cases no definite cause could be found. The most important factor seems to be the mother's attitude to breast-feeding.

WALLGREN, Stockholm.

Vitamins; Avitaminoses

THE BLOOD CONTENT OF VITAMIN A FOLLOWING ITS ADMINISTRATION TO HEALTHY CHILDREN. P. SCHIAPARELLI and P. C. GAMALERO, Minerva pediat. **7**:303 (March 10) 1955.

When 10,000 units per kilogram of body weight of vitamin A, with carotene, was given by mouth to children, the maximum amount found in the blood was reached 6 hours later; after 24 hours, the amount in the blood was no higher than before the vitamin was given. When the vitamin was given intramuscularly, the level in the blood remained high for a longer period. A persisting high level was maintained when 5000 units per kilogram was given on alternate days intramuscularly.

HIGGINS, Boston.

THE EFFECT OF VITAMIN A ON HEMOPOIESIS IN CHILDREN. P. C. GAMALERO, Minerva pediat. **7**:583 (May 5) 1955.

Thirty children with secondary anemia due either to poor diet or to recent infections were treated over a period of four to eight weeks by a combination of vitamin A and carotene. The vitamins were given orally in doses of 5000 to 20,000 units daily and also intramuscularly in an oil suspension in doses of 25,000 to 75,000 units three times a week (15,000 units per kilogram of body weight). The red blood cell counts showed a gratifying increase in 83% of the cases. The white blood cell counts tended to become normal, with a predominance of lymphocytes. Occasionally a localized reaction became manifest following the intramuscular injections but subsided without any suppuration.

HIGGINS, Boston.

VITAMIN D INTOXICATION. BJARNE ANDERSEN, Tidsskr. norske lægefor. **74**:419 (June 15) 1954.

The author reports four cases. The first was a 16-month-old girl who was given 250,000 units of vitamin D daily. After three weeks she started vomiting; after another week the appetite decreased and she developed polydipsia. She was admitted six weeks after the vitamin D treatment had started, and she had then received about 10,000 units of vitamin D. The urine showed no albumin, a few hyaline and granulated casts, red corpuscles, blood, N. P. N. 55 mg. per 100 cc., calcium 70 mg. per 100 cc., phosphorus 3.6 mg. per 100 cc., phosphatase 10 units. Roentgen examination of the skeleton and of abdomen displayed nothing abnormal. After two weeks the findings in the blood and the urine were normal, and the child was discharged healthy. The second case was a 5-year-old boy. He was admitted because of convulsions due to a chronic idiopathic hypoparathyroidism. As treatment he was given large doses of vitamin D. He received 150,000 units in four days, then 300,000 in eight days. After 14 days' treatment, the calcium content in the serum was found to be 16.2 mg. per 100 cc. The Sulkowitch test was negative. During 14 days he had received 3,000,000 units of vitamin D. The urine contained no albumin, numerous hyaline and granular casts, and no red corpuscles. Roentgen examination displayed no pathological findings. The serum findings and the urine findings became normal after two weeks. Cases 3 and 4 were siblings; a girl 3½ and a boy 2½ years of age. The girl had suffered from celiac syndrome and was treated by her physician with 70,000 units daily of vitamin D_2 for one year, with a total dose of 25,000,000 units. She suffered from diarrhea, polydipsia, polyuria, and peripheral paresis of the facial nerve. The urine contained albumin and granular and hyaline casts; the Sulkowitch test was positive. Blood calcium was 14.5 mg. per 100 cc., phosphorus 6.7 mg. per 100 cc., phosphatase 5 units, N. P. N 98 mg. per 100 cc. There was a marked hypercalcification of the metaphyses and of the whole skeleton and bilateral keratitis. During an observation time of 17 weeks, the keratitis and the paresis of the facial nerves were somewhat diminished; otherwise the findings were the same. The 2½-year-old brother was given 70,000 units of vitamin D_2 in a total dosage of 12,500,000 units. He had suffered from polydipsia, polyuria, diarrhea, and anorexia. He also had a paresis of the facial nerve of a peripheral type. There was no albumin but numerous casts in the urine. Roentgen findings of the skeleton were the same as in his sister. There was also a bilateral keratitis. The calcium content of the blood serum was 14.5 mg. per 100 cc., phosphorus 4.6 mg. per 100 cc., and phosphatase 5 units. The course of the illness was the same as in the sister.

WALLGREN, Stockholm.

Hygiene; Growth and Nutrition; Public Health

THE BASIS FOR VITAMIN T BEING A GROWTH STIMULANT. P. SALOMONE, Clin. pediat. **36**:911 (Dec.) 1954.

Observations on six babies revealed that when vitamin T was given, the amino acid content of the blood serum was lowered. Thus it would appear that a more rapid build-up of protein from amino acids would explain this finding and would be an explanation as to why this vitamin seems to stimulate growth, especially in dystrophic infants.

HIGGINS, Boston.

FATTY DEGENERATION OF THE LIVER FOLLOWING CHRONIC MALNUTRITION. L. TORRES MARTY and J. M. FRANCES ANTONIN, Arch. pediat., Barcelona **5**:257-263 (Nov.-Dec.) 1954.

This is the clinical history of a girl of 16 months who developed an illness resembling a low-grade infection. There was slight fever, green and later gray stools, loss of weight, anorexia, and edema.

The laboratory findings, x-rays and pathological sections are included. The hepatomegaly was marked. No parasitic organisms or ova could be found. The clinical examination showed gross vitamin-deficiency signs. On autopsy a typical fatty degeneration of the liver was discovered.

The differential diagnosis is discussed, and kwaskiorkor syndrome was ruled out, since the child had no changes in the skin and hair and was not anemic.

ALLEN, Santa Fe, N. Mex.

CHRONOPATHIES. GEROMINO DE MORAGAS, Acta pediát. españ. **13**:145-157 (March) 1955.

Dr. Moragas has written a very poetic discussion of the use and misuse of developmental data in pediatric practice. He states that he believes life attains its maximum beauty and authentic meaning when there is an equilibrium between the so-called norm and variation.

If all things were in the same tempo life would be as monotonous as a symphony in which all movements were the same.

Mothers with a case of indigestion due to too many lectures, books, and charts project their anxiety on their hapless children.

While believing that careful examinations and treatment should be instituted at the proper time, he feels that a lot of useless and anxiety-producing procedures may be done if the pediatrician doesn't recognize variations in maturation time.

If there must be a name for variation in maturation time, let it be called a chronopathy rather than a disease or illness. He cites many examples of slow maturation in several areas and some of the reasons in the parents' feelings for anxiety over these not serious variations. He says if man had appeared on the earth 5000 years later than he did, it would have made no difference in the history of the human race, but it would have been quite a different matter if the distance between the sun and the earth had been shorter or longer. Should we then consider some lesions as defects in time and some in space?

The author also illustrates some of his points by the use of the two verbs "to be" in Spanish—one which expresses permanence and the other the temporary state of being.

ALLEN, Santa Fe, N. Mex.

THE EFFECT OF CORTISONE ON THE BODY WEIGHT OF DYSTROPHIC INFANTS. RUTH WEGELIUS, Nord. med. **51**:878 (June 24) 1954.

Eighteen infants with celiac diseases or dystrophy associated with recurrent respiratory infections were treated with cortisone. The children were 7-19 months of age. Before starting cortisone treatment the infants were given an adequate diet and vitamins, antianemic agents, and, in case of infections, antibiotics. Cortisone was given only if the pretreatment was not successful. The effect of the treatment on the infants' general condition was remarkably good. Their weights increased, and no unfavorable side-effects were noted. In most cases follow-up studies revealed lasting improvement and diminishing tendency to respiratory infections.

WALLGREN, Stockholm.

INFANT MORTALITY RATE IN FINLAND DURING AND AFTER THE WAR. HILKKA TÄHKÄ and NIILO HALLMAN, Nord. med. **52**:1582 (Nov. 11) 1954.

The infant mortality rate in Finland in the prewar years was fairly steady (6.89%-6.78%). During the war it increased initially, reaching its peak in 1940 (8.83%). In the relatively peaceful year of 1943 it fell below 5% for the first time. Postwar infant mortality diminished gradually to 3.18% in 1952. The following factors have been of importance: stabilization of conditions after wartime upheavals, the rapid development in infant welfare work since 1944, social improvements, such as child allowances, home-sister activity, and the more effective care of the illegitimate children. In 1952, eighty per cent of all infants were controlled by the infant welfare centers.

WALLGREN, Stockholm.

Prematurity and Congenital Deformities

ARTHROGRYPOSIS MULTIPLEX CONGENITA. HAROLD G. JACOBSON, EARLE A. HERBERT, and MAXWELL H. POPPEL, Radiology **65**:8-18, 1955.

The physical, roentgenological, and pathological findings in 13 cases are described. The photographs of three are included along with roentgenograms of others. Many theories of etiology

are advanced, but the authors believe the cause to be obscure. All cases had the disease at birth. Muscle-bundle atrophy, osteoporosis, and flexion and/or extension contractures occurred in all cases. Clubfeet were present in 10 and congenital hip dislocation in 7. Other abnormal findings were calcaneal valgus deformity, clubhand, genu valgum, coxa vara, scoliosis, and spinal anomalies. Roentgenograms demonstrate the marked osteoporosis and extensive muscle-bundle atrophy as well as the deformities.

ANSPACH, Riverside, Ill.

CHONDROECTODERMAL DYSPLASIA (ELLIS-VAN CREVELD DISEASE): A CASE REPORT. JAY M. CHAUSS, Radiology **65**:213-217, 1955.

A baby girl who had the characteristics of this rare condition is described, and appropriate illustrations are included in the report. The constant findings in this condition (Caffey) are hypoplasia of the teeth and nails; progressive shortening distalward of the bones in the arms and legs; bilateral manual polydactylism and polymetacarpalism; synmetacarpalism; bilateral fusion of the capitate and hamate bones; retarded maturation of the primary ossification centers in the epiphyseal cartilages, and characteristic deformities in the proximal ends of the tibiae, proximal ends of the ulnae, and distal ends of the radii. Other changes are sometimes present but inconstant.

ANSPACH, Riverside, Ill.

A CASE OF GARGOYLISM. R. LUCCI, Minerva pediat. **7**:36 (Jan. 13) 1955.

A 3½-year-old girl presented the following characteristic findings of gargoylism; family history of consanguinity, abnormal facies, splenohepatomegaly without liver dysfunction or blood dyscrasia, mental deficiency, hypertrichosis, and a large head. She was not dwarfed, did not have kyphosis, had free movements of all her joints, and did not have corneal opacity.

HIGGINS, Boston.

PFAUNDLER-HURLER'S DISEASE AND MORQUIO'S DISEASE. MANUEL SUAREZ, Rev. españ. pediat. **11**:15-34 (Jan.-Feb.) 1955.

The author presents a case of Morquio's disease and another of Pfaundler-Hurler's disease with clinical characteristics and laboratory and x-ray studies. He also describes the genetic characteristics and concludes that they are both diseases with different forms of expression of the same genetic modifications, at least in the genetic characteristic responsible for bone maturation.

ALLEN, Santa Fe, N. Mex.

DECREASED GROWTH OF THE NECK AND UPPER AND LOWER EXTREMITIES ON A HEREDITARY BASIS. E. PUESCHEL, Monatschr. Kinderh. **103**:262-267 (May) 1955.

The author reports a family with four children exhibiting shortened neck and upper and lower extremities. This condition was traced back four to five generations. Shortening of the extremities was not marked and did not lead to markedly decreased adult body height but caused definite change of normal body proportions.

Examination of the children between 8 months and 2 years of age revealed moderate lagging behind in height in the three older patients. All four had shortened neck and upper and lower extremities. The upper extremities did not extend beyond the pubic symphysis when extended along the side of the body. The most markedly diminished body measurement was the distance between the outstretched arms.

X-rays reveal diaphyseal widening of the long bones in the children as well as the father. Cervical vertebrae were flattened. There was no radiological evidence of chondrodystrophy or other osseous defects.

HARTENSTEIN, Syracuse, N. Y.

Newborn

RENAL FUNCTION OF THE NEWBORN: AT TERM AND PREMATURE. P. ROYER, Études néo-natal. **3**:177 (Sept.) 1954.

In accordance with the findings of H. Barnett, the author's conclusions were as follows: (1) Tubular functions at birth are imperfect as far as excreting power and maximal reabsorption of certain substances are concerned. Glomerular filtration is lower than that of the adult; kidney

functions improved at the end of the first month but are completed between 6 months and 2 years, and renal immaturity is related to the degree of prematurity.

Edema in premature infants, acidosis in prematurity, and neonatal tetany are partly explained by imperfect kidney functions.

It is extremely difficult at that age to elicit definite information on an involved kidney from clinical investigations (clearance measurements are then tainted with error). The excretion of drugs taking place primarily through renal excretion (H. Barnett, Crawford), drug prescriptions should be calculated in proportion to surface area.

Penicillin G clearance calculated according to this method is much lower in the premature infant than in the adult, so that the penicillin blood level is three times higher than the adult's although the distribution volume is larger in the premature infant whose extracellular fluids are more extensive. Renal ability of the newborn infant to concentrate and dilute brings about a necessary relationship between urinary volume, urinary concentration of solids, and the amounts of solids to be excreted. This ability is quite different from that of the adult; this should be kept in mind when treating dehydration at the early age. For instance, if in a condition of dehydration with loss of NaCl only water and glucose are supplied, the extracellular hypotonic state of the premature infant will rapidly increase. Conversely, if in a case of dehydration with extracellular hypertonic state 100 cc. of saline is infused, the newborn infant will retain only 60 cc. instead of 80 cc. of water as in the case of an adult. On the other hand, easy excretion of potassium by the premature infant allows its use in the same amount as in an older infant.

Feeding problems are influenced by these facts. Under a cow's-milk diet without an additional carbohydrate supply, the newborn infant should receive, for his caloric maintenance, an amount of milk which contains an amount of salts and proteins too large for the excreting power of the kidney. Under a human milk diet these drawbacks do not exist. With the use of a powdered cow's milk it may happen that the amount of water is insufficient to allow the excretion of solids; edema ensues, with a rapid increase in weight and sometimes fever (described by Tobert Debre and Marcel Lelong as "powdered-milk fever"). An increased water intake will then induce the cessation of these troubles.

FROM THE AUTHOR'S SUMMARY.

THROMBOPLASTIN FORMATION IN THE BLOOD OF THE NEWBORN. S. VAN CREVELD, C. G. M. NAGEL, J. H. NIJENHUIS, S. I. MIRANDA, and TJON SIEN KIE, Études néo-natal. **3**:135 (Sept.) 1954.

By means of the thromboplastin generation test the formation of thromboplastin was studied in newborn full-term and in newborn premature infants.

From this study it was concluded that in newborn infants the thromboplastin formation occurs distinctly slower than in newborn full-term infants and in adults and that it takes several weeks before this thromboplastin formation in premature infants takes a normal course. It could be demonstrated that this disturbed thromboplastin formation is related to a decreased activity of a factor present in serum, probably of the P. T. C., or Christmas factor.

FROM THE AUTHORS' SUMMARY.

NUCLEAR ICTERUS OF NONERYTHROBLASTIC ORIGIN. R. MIRAPEIX TURC, Arch. pediat., Barcelona **4**:233-241 (Nov.-Dec.) 1953.

The author discusses his experiences in the study of icteric diseases at the University of Strasbourg and says there is a form of icterus gravis in the newborn which is not associated with the presence or absence of Rh-factor incompatibility.

The permeability of the hematoencephalic barrier in the newborn infant makes it possible for the central grey nuclei to become involved in the process. The physiological hyperbilirubinemia which may be even more noticeable in the premature infant may also contribute to the appearance of bilirubin in the central nervous system.

In many of these infants the symptoms may be suggestion of a true encephalitis, in others it may be manifested in the anoxemia and hypoglycemia. In cases where there is no serological evidence of incompatible antibodies (erythroblastosis fetalis) and careful differential diagnoses have been made, search should be made for any infectious process which may involve the nervous system. Early evaluation of the hypoglycemia and anoxia and treatment for this might prevent the deterioration of the nervous system in these newborn infants.

ALLEN, Santa Fe, N. Mex.

A New Theory Concerning the Mechanism of the Initiation of Respiration in the Newborn. S. Jaykka, Acta pædiat. **43**:399 (Sept.) 1954.

A new theory to explain the opening mechanism of the lungs has been advanced: it has been proved experimentally that expansion of the pulmonary alveoli is caused by capillary erection which is effected by the initiation of the pulmonary circulation. The theory propounded does not contradict previous observations which refer to the phenomena in fetal and neonatal lungs; these can be built into it, and intricate problems, previously unexplained, may find in it a rational explanation. The peculiarity of the fetal circulation has long been known, but an explanation for its function has not been produced. Such an explanation as "The ductus arteriosus thus serves during fetal like as a means of balancing right and left cardiac output and in so doing, acts as what might be called the exercising channel of the right ventricle" (Patten), can hardly be sufficient. With the help of the author's theory the reason for the existence of the foramen ovale and ductus arteriosus is explained quite easily. They are indispensable in preventing the initiation of blood flow and the increase of blood pressure in the pulmonary circulation. The author states that he has not found this explanation described in earlier literature, and it should, consequently, be considered a new one.

From the Author's Summary.

Acute Infectious Diseases

Tuberculous Meningitis: The Diagnostic and Prognostic Significance of Spinal Fluid Sugar and Chloride. H. W. Gierson and Joseph I. Marx, Ann. Int. Med. **42**:902, 1955.

Gierson and Marx report their observations in 231 cases of tuberculous meningitis from the standpoint of recovery based upon the spinal fluid sugar and chlorides. The chlorides were diminished with greater frequency than was the sugar. It was found that, of the two factors, the reduction of chlorides is more reliable, but neither provides a sensitive prognostic index. The authors recommend, however, that chloride determinations be continued as part of routine spinal fluid analysis in tuberculous meningitis.

Mandel, Philadelphia [A. M. A. Arch. Neurol. & Psychiat.].

Canicola Fever with Neurological Complications. J. E. Middleton, Brit. M. J. **2**:25 (July 2) 1955.

Middleton reports a case of canicola fever contracted from a pet dog in which treatment with chlortetracycline cured the infection but convalescence was complicated by cervical radiculitis, characterized by paralysis of the right serratus anterior and right diaphragm, transient paresis of the left thumb, and initial subjective sensory changes over the left forearm. Complete recovery did not occur until 18 months after onset of the illness. Middleton points out that, although neurological symptoms are common in canicola fever, neurological complications are rare. He believes that the case reported is a further example of the shoulder-girdle syndrome, presumably due to hypersensitivity reaction to the infection.

Echols, New Orleans [A. M. A. Arch. Neurol. & Psychiat.].

The Duration of Immunity Following Vaccination with Diphtheria Anatoxin. A. Rosa, R. Olivo and M. La Placa, Clin. pediat. **36**:746 (Oct.) 1954.

The titer of diphtheria antitoxin in the blood sera of a group of children in Emilia, Italy, was determined. Each of the children had received an approved course of anatoxin prophylaxis before he was 2 years old. It was found that about 80% of the 2-year-old children had an adequate immunity; this percentage had dropped to 41% in the 4- to 5-year-old group; there was a rise to 59% in the 7-year-old group, and to 80% in the 10- to 13-year-old group.

Therefore, it is obviously desirable that the injections of anatoxin be repeated at the time the child enters school (booster dose). The figures given apply to the one city studied; it is very probable that they will vary for different localities, since the amount of antitoxin in the blood will depend upon the degree of exposure to diphtheria organisms and whether there are many carriers in the community.

Higgins, Boston.

THE BODY WEIGHT, THE R.B.C. SEDIMENTATION RATE, AND THE ALLERGY TO TUBERCULIN OF CHILDREN WITH HILAR OR JOINT TUBERCULOSIS, AS AFFECTED BY CLIMATIC CHANGES. V. MIONE and F. MULÉ, Clin. pediat. **36**:762 (Oct.) 1954.

One hundred seventy-one children with hilum or joint tuberculosis were transferred for the summer months from a sanatorium 120 m. above sea level to a mountain resort 800 m. above sea level, with an average barometric pressure of 701 mm. The change allowed for more heliotherapy and more comfortable temperature conditions. It was found as a result of the change that (1) the children gained in weight, (2) there was an increase in the degree of allergy to tuberculin, and (3) the sedimentation rate tended to fall to normal figures.

HIGGINS, Boston.

A CLINICAL, RADIOLOGICAL, AND TUBERCULIN EVALUATION OF SUBJECTS TEN TO FOURTEEN YEARS AFTER VACCINATION WITH PETRAGNINI'S ANATUBERCULIN. L. F. SIGNORINI and C. PANERO, Clin. Pediat. **36**:899 (Dec.) 1954.

A group of 175 individuals who had been vaccinated in 1939 to 1943 with Petragnini's anatuberculin were studied; interval histories were taken, physical examinations made, and chest x-ray films and tuberculin tests made. A group of 66 siblings who had not been vaccinated served as controls; 81% of the vaccinated subjects showed positive tuberculin reactions, as compared with 67% of the siblings. Histories and examinations revealed the vaccinated group were healthier and had had fewer illnesses; their chest x-rays were clearer. Only two of the vaccinated group had had severe illnesses due to tuberculosis. The writers believe that this is a remarkable record, considering that many of the subjects had been exposed to active cases of tuberculosis.

HIGGINS, Boston.

TYPES OF BACTERIAL INFECTIONS AND MODE OF REACTION IN VARIOUS AGE GROUPS OF CHILDHOOD. BO VAHLQUIST, Nord. med. **51**:262 (Feb. 18) 1954.

The influence of age in the susceptibility to and course of infectious diseases has so far attracted only limited attention. The author discusses some clinical aspects in relation to diseases of the upper respiratory tract and the intestines. Some figures for bacterial meningitis are included. It is pointed out that the different types of reactions in different age groups are obviously related to age differences in morphological structure and in physiological function, including specific and nonspecific antibacterial protective mechanisms.

WALLGREN, Stockholm.

BACTERIAL INFECTIONS IN CHILDHOOD. GUNNAR LAURELL, Nord. med. **51**:265 (Feb. 18) 1954.

The characteristics of some bacterial infections in infancy are discussed, especially epidemic infantile gastroenteritis and skin lesions. The conclusion drawn is that the child has its own way of reacting to infections.

WALLGREN, Stockholm.

BACTERIAL INFECTIONS IN CHILDHOOD. G. TUNEVALL, Nord. med. **51**:267 (Feb. 18) 1954.

The author reports 550 cases of respiratory infections without purulent complications. Each of the four commonest bacterial agents (pneumococci, hemolytic streptococci, Hemophilus influenzae, and pyogenic staphylococci) has its age of predilection in childhood: pneumococci during the first two years, streptococci especially common after the second year, and Hemophilus influenzae during the first two to three years of life. It is also shown that the average antibody titers as well as the ability to produce antibodies in acute infections rise with increasing age. This development proceeds, however, at different rates for different antibodies, the rate being determined by the age predilections mentioned. A weak antibody formation against pneumococci and influenzae bacilli was associated with a tendency to recurrence of otitic suppurations due to those bacteria.

WALLGREN, Stockholm.

TUBERCULOUS MENINGITIS. JAKOB BJØRNSTAD, Nord. med. **51**:273 (Feb. 18) 1954.

This is a report of 228 cases of tuberculous meningitis occurring in the city of Oslo during the period 1929-1950. From the period 1929-1934 to the period 1943-1950 there was a decline of the incidence in all age groups. The decline on the whole was 77.3%. It may be explained by reduction of the infection risk in childhood. No definite statement can be made regarding the reduction of the morbidity rate by BCG vaccination.

WALLGREN, Stockholm.

PUBLIC HEALTH ASPECTS OF INFECTIOUS HEPATITIS. HAAKON NATVIG and ROALD ADELSTEN-JENSEN, Nord. med. **51**:432 (March 25) 1954.

This report is based upon cases seen in Norway between 1942 and 1948. The attack rate of infectious hepatitis was observed to be higher in rural than in urban districts during the epidemic wave in the first five years of the observation period. In the last two years of the period, however, higher morbidity rate was found in the urban population; the disease also became more serious from year to year. The attack rates were highest in the age group 20-39. In 52 cases the probable source of infection could be detected, and examples are given of transmission by personal contact as well as of food-borne and water-borne infections. The authors stress the importance of compulsory notification and of an intensification of the control measures against this potentially serious disease. About 70 cases of probable inoculation hepatitis were seen. The attack rate in age groups under 20 is less than that of infectious hepatitis. The inoculation hepatitis was frequent among physicians and hospital personnel. Most of the patients had had inoculations or blood tests in hospitals or outpatient departments and laboratories, blood tests, blood transfusions, and operations being the most common source of infection.

WALLGREN, Stockholm.

ACUTE BACTERIAL MENINGITIS. J. A. GRÖNROOS and PIRKKO UURASMA, Nord. med. **51**:846 (June 17) 1954.

The authors report on 92 cases of acute meningitis of which the bacteriological diagnosis was confirmed in 73 cases: Hemophilus influenzae 22, pneumococcus 26, meningococcus 14, and various other bacteria 11. Comparison with previous series suggests that the incidence of meningitis due to Hemophilus influenzae has increased and that due to hemolytic Streptococcus has decreased. In the present series there were 13 different types of pneumococci found. The fatality rate in the present series was 33%, greatest in the youngest age group and for pneumococcus meningitis. To improve the prognosis, early clinical and bacteriological diagnosis is required, as well as treatment based on the etiology. Routine intrathecal treatment should be avoided, since oral, intramuscular, or intravenous administration of effective doses is more reliable. Meningitis due to penicillin-sensitive bacteria should be treated with large doses of penicillin and sulfonamides. Chloromycetin has proved to be very effective in treatment of meningitis caused by Hemophilus influenzae.

WALLGREN, Stockholm.

A HOUSE EPIDEMIC OF ATYPICAL PNEUMONIA IN CHILDREN. CARSTEN WILDT-ANDERSEN, Nord. med. **52**:1121 (Aug. 12) 1954.

Fourteen of thirty-three children living in the same building as a 6-year-old girl with severe primary atypical pneumonia presented more or less characteristic respiratory tract symptoms. The cold agglutination titer was positive in three, with fluctuations of the titer in two. The serological examinations were not carried out, however, at the most favorable junction.

WALLGREN, Stockholm.

Chronic Infectious Diseases

RESULTS OBTAINED IN THE TREATMENT OF TUBERCULOUS MENINGITIS (1947-1952). G. CASCIO and R. PURPURA, Pediatria **62**:511 (July) 1954.

An analysis is made of the cases of 420 children with tuberculous meningitis seen over the six-year period 1947-1952 at the pediatric clinic in Palermo, Sicily. The rates of incidence and mortality (19% and 50%) were highest in the infants under 1 year of age and fell gradually as the children grew older until in the 9-year-old children the rates were 3.5% and 12%. Fifty per cent of the children had hilum gland tuberculosis and 5% miliary tuberculosis; 37% of the children showed no other localized tuberculous lesions. In 1947, the year when streptomycin was first used, the percentage of cures was 15%; in 1948 it was 30%; in 1949 46%. In 1950, when PAS supplemented the streptomycin therapy, the rate was 50%; in 1951, with streptomycin and thiosemicarbozone therapy, 63%, and in 1952, with streptomycin and isoniazid, 71%.

HIGGINS, Boston.

FREE AMINO ACIDS IN CEREBROSPINAL FLUID IN TUBERCULOUS MENINGITIS. R. ROSSI, I. NICOLETTI, and G. RAPI, Riv. clin. pediat. **53**:519, 1954.

The authors have made researches with a chromatographic method on paper disc upon the behavior of free amino acids in the spinal fluid of patients with tuberculous meningitis, both in the lumbar region and the underoccipital region, during the course of the disease. The various technical methods followed during the period of research are first described, then the behavior of the amino acids found is related; with the method chosen it is possible to note the increase of the concentration of only 6 amino acids, in comparison with the 11 generally found in the spinal fluid. After having interpreted the origin of these amino acids, the authors end by including them in the framework of the vast picture of the meningeal permeability.

FROM THE AUTHORS' SUMMARY.

PROPHYLAXIS AGAINST TUBERCULOSIS WITH B.C.G. F. GONZALES FUSTE and C. SOLER DURALL, Arch. pediat., Barcelona **5**:143-160 (Sept.-Oct.) 1954.

This is a report from the Municipal Laboratory of Health in Barcelona. The uses of B.C.G. most effective from the public health standpoint are discussed. The mode of administration, both in private patients and mass clinics, is described.

The method of preparation at the Barcelona Municipal Laboratory is described. This laboratory is one of the oldest in the world.

ALLEN, Santa Fe, N. Mex.

TUBERCULOSIS OF THE PHARYNX AND ITS RELATION TO THE GENERAL CONCEPT OF TUBERCULOUS INFECTION. R. POCH VIÑALS, Arch. pediat., Barcelona **5**:249-282 (Nov.-Dec.) 1954.

The author reviews the literature on what is undoubtedly a rare form of tuberculosis. He feels that there is a definite constitutional factor even when children are removed from parents having the disease at an early age. He would not, however, say it is inherited or congenital other than that there is a certain tendency toward susceptibilty. The organism may be of a human or bovine type. The adenitis called a primary infection is merely a spreading to contiguous tissues of a pharyngeal infection.

He discusses the pathology and includes several pathological sections and shows the tendency toward healing spontaneously at the site of the mouth or tonsillar lesion with subsequent spread by lymphatics to the lymph nodes of the neck.

He also describes the treatment. Most lesions disappear by the eighth month of treatment.

ALLEN, Santa Fe, N. Mex.

THREE CASES OF BRAIN TUBERCULOMA. LUCRETIA HERNANDEZ, Rev. peruana pediat. **12**:26 (July-Dec.) 1953.

Three cases of tuberculoma of the brain are reported. The first case had remarkable neurological symptoms suggesting tuberculous meningitis; postmortem examination revealed widespread tuberculomas. The second case had endocranial hypertension suggesting brain tumor. At autopsy a tuberculoma involving left internal capsule and left lenticular nucleus was found; this localization is rare. The third case had endocranial hypertension and neurological symptoms of sensorial involvement suggesting damage of the right parietal zone. A tuberculoma was removed from that zone surgically. This paper shows the high percentage of tuberculomas of the brain in childhood and the protean clinical and anatomical features.

FROM THE AUTHOR'S SUMMARY.

IS EXUDATIVE TUBERCULOUS PLEURISY A SEASONAL DISEASE? K. HARTUNG, Monatssch. Kinderh. **102**:370-371 (Aug.) 1954.

Among 155 children with exudative tuberculous pleurisy, 92 had the onset of their disease during the first six months of the year and 51 between April and June. On the basis of these figures, the author felt that this form of tuberculosis could be considered as seasonal, namely spring, which is the case for most forms of tuberculosis.

HARTENSTEIN, Milwaukee.

THE ELECTROENCEPHALOGRAM IN TUBERCULOUS MENINGITIS IN CHILDHOOD AFTER TERMINATION OF TREATMENT. R. GARSCHE, Ztschr. Kinderh. **75**:613, 1955.

Electroencephalographic studies in children following successful treatment of tuberculous meningitis show increased slow waves, appearance of waves of high frequency (β-activity), and convulsive patterns. Return to normal occurs often only after several years, and the changes are severer and longer lasting in the chronic cases of tuberculous meningoencephalitis. Some phenomena appear only after termination of treatment. The explanation for the electroencephalographic changes are diffuse vascular processes and scars.

GLASER, Baltimore.

COMPLICATIONS FOLLOWING INTRACUTANEOUS INOCULATION OF NEWBORN INFANTS WITH BCG VACCINE. J. I. DE BRUIJNE, S. VAN CREVELD, M. R. H. STOPPELMAN, R. VAN PUTTEN, and O. A. TERPSTRA, Nederl tijdschr. Geneesk. **98**:1290 (May 8) 1954.

In the period March, 1951, to February, 1952, the number of newborn infants inoculated intracutaneously with BCG vaccine was 1949. During the first months a dosage of two injections of 0.1 ml. each was used. Because many suppurations of regional lymph nodes were noted, the dosage was reduced to 0.05 ml. twice and later on to two injections of 0.03 ml. of the vaccine.

Of the 809 infants who were inoculated with 0.1 ml. of BCG vaccine in either arm, 748 were followed up. Suppuration of one or more nodes occurred in 14.3%. In some cases the suppuration was first seen 12 to 15 months after the inoculation. Of the group of 681 children inoculated with 0.05 ml. on either side, 634 were followed up. Suppuration was seen in 3% of this group.

In the group of 459 infants who received 0.03 ml. of BCG vaccine twice, suppuration of lymph nodes was seen in 4% of the 422 children who were examined 11 to 15 months after the inoculation. At that time the tuberculin skin test proved to be positive in 98.4%.

VAN CREVELD, Amsterdam.

LONG-LASTING EXPERIENCES IN INFANTS WITH CONGENITAL SYPHILIS TREATED EXCLUSIVELY WITH PENICILLIN. S. E. BOS, J. I. DE BRUIJNE, and W. M. VAN WERMESKERKEN, Nederl. tijdschr. Geneesk. **98**:2060 (July 24) 1954.

Since 1947, infants in Amsterdam with congenital syphilis are no longer treated with arsenic or bismuth but exclusively with one two-week course of penicillin, 150,000-200,000 units per kilogram of body weight. A physical and psychiatric follow-up study and the control of the serological syphilis test of the 27 children treated in this way revealed favorable results. There proved to be no more need for a combined treatment with arsenic or bismuth. In all children the serological tests became negative. There seemed to be a correlation between the age of the beginning of the treatment and the time that elapsed before the serological tests became negative. There were five deaths, one as a result of a Herxheimer reaction. On account of this risk the dosage is low during the first days of treatment.

VAN CREVELD, Amsterdam.

Diseases of Blood, Heart and Blood Vessels, and Spleen

STRUCTURAL CHANGES IN INTRAPULMONARY ARTERIES EXPOSED TO SYSTEMIC PRESSURES FROM BIRTH: REPORT OF A CASE OF TETRALOGY OF FALLOT WITH A WIDELY PATENT DUCTUS ARTERIOSUS AND AN ANOMALOUS RIGHT PULMONARY ARTERY ARISING FROM THE CELIAC AXIS. CARLOS TEJADA VALENZUELA, JULIO TORIELLO, and WILBUR A. THOMAS, A. M. A. Arch. Path. **57**:51 (Jan.) 1954.

The case presented is of a baby boy who entered the hospital at the age of 2½ months because of recurrent cyanosis and retarded growth. He was kept in the hospital for the subsequent 3½ months, showing little change. At the age of 6 months it was apparent that survival was unlikely without some improvement in the oxygenation of blood. An operation was performed with transection of the left pulmonary artery and an end-to-end anastomosis to an anomalous right subclavian artery arising from the posterior aspect of the arch. A few minutes after the anastomosis was completed, the heart stopped and independent contractions could not be reestablished. Gross anatomical findings were a tetralogy of Fallot with a widely patent ductus arteriosus, an anomalous branch of the celiac axis to the right lung (lower lobe), absence of the middle lobe of right lung, agenesis of the left kidney, and incomplete rotation of the colon. Microscopic findings of most unusual note were present in the lungs, which showed marked muscular thickening

unassociated with intimal sclerosis of the small pulmonary arteries. In addition, multiple organized, recanalized emboli (from a mural thrombosis in the right ventricle) were found in many of the pulmonary arterioles and small arteries of the left lung. The authors compared the vascular changes with those seen in normal circulatory systems and in a case of tetralogy of Fallot with a closed ductus arteriosus. All of these controls had thin-walled arteries. The authors, therefore, explained the thick-walled vessels of this case on the basis that pulmonary artery pressures were equivalent to those in the systemic circulation, and, hence, the small arteries and arterioles retained their fetal appearance. The changes associated with pulmonary hypertension acquired later in life, as in mitral stenosis, are quite different. These consist of intimal sclerosis without striking changes in the muscular coats.

CHAN, San Francisco.

ANEMIA IN ALASKAN ESKIMOS. E. M. SCOTT, RITA C. WRIGHT, and BARBARA T. HANAN, J. Nutrition **55**:137 (Jan. 10) 1955.

The authors found that over a considerable area of Alaska the Eskimo population is moderately anemic by the usual standards. The anemia is often microcytic and hypochromic, and mostly men have a moderate normochromic, normocytic anemia. The data suggest that iron deficiency and some other factor were responsible for low hemoglobin levels found in Eskimos. The second factor may cause the widespread, moderate normocytic anemia, while in those cases where iron requirement is high, an iron-deficiency anemia is superimposed. No direct evidence of a second factor has as yet been obtained.

FREDEEN, Kansas City, Mo.

EPILOIA AND ENDOCARDIAL FIBROELASTOSIS. L. CROME, Arch. Dis. Childhood **29**:136 (April) 1954.

Two cases of epiloia showed endocardial fibroelastosis in addition to more familiar changes in the brain and other organs. This association is discussed, and it is suggested that the structural change, fibroelastosis, may occur in a number of conditions other than the disease bearing that name and is not necessarily a disease sui generis. Perivascular reticulation and adventitial hypertrophy were present in the cerebral white matter of one of the cases, a finding not hitherto recorded in epiloia.

KELLY, Milwaukee.

THE INVESTIGATION OF A LARGE FAMILY AFFECTED WITH VON WILLEBRAND'S DISEASE. J. C. W. MACFARLANE and M. J. SIMPKISS, Arch. Dis. Childhood **29**:483 (Dec.) 1954.

Von Willebrand's disease is characterized by a tendency to bleed, especially in form of recurrent epistaxis and intractable hemorrhage following dental extractions, accompanied by a normal coagulation time, no reduction in the number of platelets, a prolonged bleeding time, and, in the one case so investigated, efficient clot retraction. In this particular family both sexes were affected, the disease being inherited as a Mendelian dominant, but while the disease in females appeared to be either severe or mild in degree, the males were all affected to the same moderate degree. Von Willebrand and his colleagues sought to prove that in this condition the platelets were qualitatively deficient.

In this study a family of 64 members, extending over five generations and containing 21 affected members, is recorded.

KELLY, Milwaukee.

Diseases of Nose, Throat, and Ear

DIFFUSE EXTERNAL OTITIS: PATHOGENESIS AND TREATMENT. BEN H. SENTURIA, Laryngoscope **65**:313 (May) 1955.

In order to understand external otitis, the anatomy and physiology of this region must be understood. The kind of skin and glands present is particularly important. Senturia reviews these structures in detail. The physiology of the glands as well as the nature of the secretions is also considered.

Normal subjects in hot humid atmosphere were observed. Very little cerumen was noted, probably because of frequent swimming and the rapid spread of the lipids on the warm, moist skin. Heat and high humidity may cause a change in the pH toward the alkaline side, with resultant hyperkeratosis and plugging of the glands. All these are factors in the etiology of external otitis. Senturia then reviews the histopathology of this condition.

Therapy should include the following: (1) prophylaxis in susceptible persons during hot humid weather and (2) topical and/or systemic treatment early. This should be soothing and palliative in the mild stages and active and curative in the severe stages.

Included in the above are removal of the patient from the hot humid weather, cleansing of the ear canal, and application of mild astringents and drying solutions and nonirritating antipruritics combined with antibiotics of low-sensitivity index. In the severer cases, the antibiotics should be used systemically and a wool fat (lanolin) or glycerin pack inserted into the ear canal for 24 hours to reduce the edema. Cleaning treatment should be continued throughout.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

PURE-TONE AUDIOMETRY FOR PRESCHOOL CHILDREN. BENGT BARR, Nord. med. **51**:464 (April 1) 1954.

The author has performed pure-tone audiometric investigations on about 300 children 1-6 years of age. Both psychogalvanic skin-resistance (PGSR) audiometry and play audiometry were used. The procedures followed and the results obtained with the respective methods are discussed and compared. It was possible to use play audiometry on normally developed children as young as 2½ to 3 years of age. PGSR audiometry could be used on even younger children. The threshold values obtained were considered reliable when two audiograms showed agreement; assuming a difference of not more than 5 db. as permissible, the two methods showed full agreement in 85% of the threshold determinations. Follow-up examinations performed one to two years later showed practically unchanged values. The author is of the opinion that in cases where play audiometry can be carried out it should be the method of choice.

WALLGREN, Stockholm.

Diseases of Lungs, Pleura, and Mediastinum

AN ANALYSIS OF TWO HUNDRED FIFTEEN CASES OF BRONCHIECTASIS. G. E. LINDSKOG and D. S. HUBBELL, Surg., Gynec. & Obst. **100**:643 (June) 1955.

The authors present data from a series of 215 consecutive cases of proved bronchiectasis, with particular reference to age at onset of the disease and at time of treatment, sex, race, recognized etiologic factors, chief symptoms, anatomic distribution of the disease by lobes and segments, and bacteriology of the sputum. The criteria for selection of patients for surgery are given. Of 165 pulmonary resections of various types carried out on 138 patients, there were 4 hospital deaths, an operative mortality of 2.4%. Follow-up data as well as factors influencing the prognosis of bronchiectasis are discussed. It is interesting to note that of the 214 patients, sinusitis was demonstrated in 74. The cases associated with sinusitis seemed to have an equally good prognosis after resection, whether or not special therapy was directed against the sinus disease before or after surgery.

FRIEDBERG, Chicago [A. M. A. ARCH. OTOLARYNG.].

SUCCESSFUL TREATMENT OF PRIMARY SUPPURATIVE PNEUMONIA IN INFANTS. W. FREISLEDERER, Deutsche med. Wchnschr. **80**:1348-1350 (Sept. 16) 1955.

Six infants with primary suppurative pneumonia were treated with hydrocortisone or Decortin in addition to antibiotics. The dosage of peroral hydrocortisone was 20-30 mg. per day; that of Decortin, 10-15 mg. per day, with gradual reduction in the course of 4 to 12 days. When this treatment was given for more than a week it was followed by 12.5 mg. ACTH for two days. The suppurative pneumonia was very severe. The severe circulatory collapse yielded readily. In some cases the pneumonic and pleural lesion also responded well; in some the delayed treatment did not have this effect.

AMBERG, Rochester, Minn.

A NEW STABLE ANTIGEN FOR THE SERODIAGNOSIS OF THE INTERSTITIAL PLASMA CELL PNEUMONIA OF YOUNG INFANTS AND PREMATURE INFANTS. O. VIVELL, Deutsche med. Wchnschr. **80**:1357 (Sept. 16) 1955.

A method, based on that of Casals, is described for the preparation of a stable antigen from the lung of an infant who died from interstitial pneumonia. With this antigen the complement-fixation test for interstitial pneumonia in young and premature infants is advanced greatly.

AMBERG, Rochester, Minn.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

VIRUS HEPATITIS IN INFANTS: ITS EPIDEMIOLOGY, ITS CLINICAL COURSE, AND THE HISTOLOGICAL CHANGES IN THE LIVER. F. DE MATTEIS, Clin. pediat. **36**:101 (Feb.) 1954.

Three cases of virus infectious hepatitis in infants 2 to 4 months of age are reported. Biopsies of the liver were done in each case at various stages of the disease. Early in the disease there are present marked injury to the liver tissue and areas of inflammation in the parenchyma; later, with the diminution of cellular infiltration, sclerosis gradually develops. Some of the parenchymal cells take on the appearance of glycogen-storage-disease cells, but they give reactions for neither glycogen nor fat.

HIGGINS, Boston.

FUNCTIONAL STENOSIS OF THE ESOPHAGUS. L. LANDUCCI, Lattante **25**:37 (Jan.) 1954.

A 3-year-old girl had a functional stenosis of the esophagus. Various therapeutic procedures were tried and proved inefficacious. Finally the vomiting was controlled by phenobarbital, and the child's nutrition and general condition improved.

HIGGINS, Boston.

THE LIVER FUNCTION IN INFECTIOUS HEPATITIS. N. POMPONIO, Pediatria **62**:96 (Jan.) 1954.

During an epidemic of infectious hepatitis at the University Clinic in Naples, 50 children contracted the disease. The Takata-Ara test was done at intervals on each child. In healthy children, the test showed its maximum intensity for an individual on the 15th to the 20th day after the onset of the jaundice; it became negative by the 35th day. In undernourished or syphilitic children, the intensity of the reaction was greater, reaching the maximum intensity on about the 30th day, and became negative on about the 60th day.

HIGGINS, Boston.

HISTOLOGICAL FINDINGS IN THE LIVER OF CHILDREN WITH MALNUTRITION, AND ESPECIALLY WITH RIBOFLAVIN DEFICIENCY. A. ALBEGGIANI, Pediatria **62**:175 (March) 1954.

Biopsies by liver puncture were made on 17 young children with nutritional disturbances; many of them had diarrhea. Steatosis, or fatty degeneration, was the usual finding. As the condition of several of the children improved, biopsies were repeatedly done on the liver, and it was found to reassume gradually a normal structural picture histologically. It seems quite likely that vitamin B deficiency, and especially riboflavin deficiency, was a major cause of the steatosis; it is probable that the intestine failed to absorb the vitamin.

HIGGINS, Boston.

GASTRODUODENAL ULCERS IN CHILDREN. G. CANESTRI, Pediatria **62**:247 (March) 1954.

Reports are given of the cases of 4 children, 8 and 9 years of age, admitted to a hospital in Alexandria, Egypt, in a period of six months with duodenal ulcers. The author believes that the condition is much more frequent in children than reported in the textbooks. Some cases are erroneously diagnosed as appendicitis and even operated upon. Vomiting is a frequent symptom of the condition in children. Also, children usually can not describe their symptoms as clearly as can an adult. In general the course and treatment in children are the same as in adults. Each of the children in this report was extremely emotional.

HIGGINS, Boston.

EARLY RECURRENCE OF ACUTE INTUSSUSCEPTION. ERIK CHRISTENSEN, Nord. med. **52**:1732 (Dec. 9) 1954.

Reports have been made of 86 cases of early recurrences of acute intussusceptions in children. The author adds two new postoperative cases in infants aged 5 and 6 months, respectively. Early recognition of this rare condition is of paramount importance, and prompt operative intervention is the best treatment. In the first case a new attack of intussusception started three days after a successful reposition of a first attack. The child was discharged healthy. In the second case a new attack of intussusception occurred three months after a successful reposition of the first attack. Even the second recurrence of the intussusception was successfully reposited and the child discharged healthy.

WALLGREN, Stockholm.

Nervous Diseases

CASE OF ACROMEGALY ASSOCIATED WITH THYROTOXICOSIS. JOHN P. HEANEY, CHARLES L. JAMES, CHARLES L. SPURR, and MICHAEL E. DEBAKEY, A. M. A. Arch. Surg. **71**:279 (Aug.) 1955.

The authors report in detail a case of acromegaly combined with thyrotoxicosis. It is noteworthy that more than one-half the patients with acromegaly show significantly increased basal metabolic rates and one-fourth exhibit an enlarged thyroid gland. The problem whether the thyrotoxicosis is an independent, coexisting condition or is secondary to hyperpituitarism has not been conclusively solved. Hypermetabolism found in cases of acromegaly cannot be explained by the presence of an associated hyperthyroidism, but is to be considered due in part to direct action of the overfunctioning pituitary gland, for the following reasons: The radioactive iodine uptake in true hyperthyroidism is high, whereas in cases of acromegaly with hyperthyroidism it remains usually normal or low. The circulating protein-bound iodine is not elevated in acromegaly, in contrast to that in cases of true thyrotoxicosis. Hyperthyroid symptoms in acromegaly frequently fail to respond to strong iodine solution U. S. P. and to thiourea derivatives.

The increased metabolism of acromegalics may be reduced either by surgery or by irradiation of the pituitary gland. In the absence of serious pressure symptoms from pituitary tumor or from thyromegaly, it is advisable to begin the treatment with x-ray therapy of the pituitary gland. If this fails, the patient should then be subjected to total thyroidectomy, following adequate preparation with strong iodine solution U. S. P. Acromegalic patients with an enlarged larynx are more likely to need temporary tracheotomy than the average patient with thyroidectomy. There is no evidence that thyroidectomy will increase the acromegalic symptoms.

LIST, Grand Rapids, Mich. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

FATAL TOXIC ENCEPHALITIS OCCURRING DURING IPRONIAZID THERAPY IN PULMONARY TUBERCULOSIS. ROGER S. MITCHELL, Ann. Int. Med. **42**:417 (Feb.) 1955.

Mitchell describes a case of fatal toxic encephalitis which occurred after six months of iproniazid therapy in a 4 to 5 mg/kg. dose. The patient was a 60-year-old man who had been treated for pulmonary tuberculosis over a period of 20 years by intermittent bed rest, aminosalicylic acid, streptomycin, and pneumoperitoneum.

For three months preceding his final acute illness the only drug taken regularly was iproniazid. There was a striking change in his appetite and in his mood, which became almost euphoric, in contrast to his usual rather anxious and depressed state. The remarkable increase in appetite resulted in a gain of 30 lb. Other symptoms, suggestive of a mild toxic effect on the central nervous system, were not considered troublesome by the patient. These were slight tremor in the arms and legs, increased frequency of urination with some urgency, continued reduction in potency, which was already declining, some restlessness at night, and some tinnitus.

The final illness began acutely with rise in temperature, and the possibility of a tuberculous meningitis was considered because of the developing double vision, increasing headache, and motor restlessness. This clinical impression was later altered to meningoencephalitis. The patient became increasingly toxic and died 10 days after the onset of the terminal episode.

Postmortem examination was limited to the brain. There was no evidence of tuberculosis in either the brain or the meninges. The anatomic diagnoses were slight focal leptomeningeal scarring; focal subarachnoid hemorrhages; focal perivascular fresh hemorrhages in the cerebral cortex and hemosiderin deposits about the parenchymal vessels and in the meninges; slight perivascular mononuclear infiltrations associated with hemorrhage in the brain stem and cerebrum; occasional hyaline intracerebral vessels, and chromophobe adenoma, hypophysis.

Since there was no other obvious cause of toxicity, it seems reasonable to attribute the patient's death to hemorrhagic encephalitis due to a toxic effect of iproniazid.

There was one other death of a patient receiving iproniazid at Trudeau Sanatorium. In this case there was no demonstrable relationship between death and the drug. A 50-year-old man with moderately advanced pulmonary tuberculosis died very suddenly, without any warning whatsoever, on the eighth day of iproniazid therapy (4 mg/kg.). A complete autopsy, including the brain, revealed no cause for death. It was presumed that death was due to ventricular fibrillation.

The author suggests that, in view of the similarity of the symptoms displayed by these patients to those resulting from acute vitamin deficiency, the possibility exists that the two deaths reported may have occurred because of acute nicotinamide deficiency induced by iproniazid therapy.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

CEREBRAL HEMISPHERECTOMY FOR CONTROL OF INTRACTABLE CONVULSIVE SEIZURES. L. A. FRENCH, D. R. JOHNSON, I. A. BROWN, and F. B. VAN BERGEN, J. Neurosurg. **12**:154 (March) 1955.

Cerebral hemispherectomy was used in eight institutionalized children who had infantile hemiplegias with intractable seizures. This operation was an outgrowth of the procedure used to control seizures in a 38-year-old man with status epilepticus following removal of a left parietal glioma. The ages varied from 13 to 38 years, and each case was studied by pneumoencephalography or arteriography, which revealed evidence of a dilated ventricle on the affected side, porencephalic cysts, or atresia of the middle cerebral vessels. At operation, all the structures peripheral to the thalamus were removed, and great care was taken to insure removal of the hippocampus and orbital gyrus. The gross abnormalities included meningeal scarring, subarachnoid cysts, and extensive vascular malformations.

All patients except the man with the glioma previously mentioned had had uncontrollable seizures that made institutionalization necessary. Four patients have had no seizures and are not receiving medication. Three others have had one seizure each, all occurring within the first few months after operation, and each is now taking only small doses of anticonvulsants. One patient had five seizures postoperatively, but none within the last two years, and the last case was regarded as a failure, that of a microcephalic adolescent of 17 who averaged 700 to 800 grand mal seizures yearly, but still continued to have 70 seizures yearly in spite of hemispherectomy. The operation had no effect upon any preexisting neurological deficits, nor did it result in any intellectual impairment. Many patients have shown a definite improvement in their personality adjustment.

MANDEL, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

PERITONEAL SHUNTS IN THE TREATMENT OF HYDROCEPHALUS AND INCREASED INTRACRANIAL PRESSURE. IRA J. JACKSON and S. R. SNODGRASS, J. Neurosurg. **12**:216, 1955.

Jackson and Snodgrass report their results in the treatment of increased intracranial pressure in 62 patients over a four-year period. The ages varied from 3 days to 65 years, but the majority were under 14 years of age. The patients were treated by ventriculoperitoneal or by lumbar subarachnoid shunts. The complications were many, but blockage of the tube within the abdominal cavity by either omentum or scar tissue occurred most frequently. Obstruction by small amounts of cerebral tissue was less frequent in the cranial portion of the tube. Postoperative infection, kinking of the tube, and hypotensive headaches were the other complications encountered.

The more successful shunts were in patients with a diagnosis of infantile hydrocephalus or pseudotumor cerebri. Only 24 patients in this series had shunts which functioned over one year, and the longest was a single shunt which had functioned four years at the time of the report. The authors state from their experience that the longer these patients are followed, the poorer are the long-term results. Shunt operations have a very definite, but limited, value in the neurosurgeon's armamentarium.

MANDEL, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

MESTINON IN THE TREATMENT OF MYASTHENIA GRAVIS. M. R. WESTERBERG and K. R. MAGEE, Neurology **4**:762, 1954.

Twenty-two patients with myasthenia gravis were given Mestinon bromide. Their ages ranged from 17 to 64 years; there were 16 female and 6 male patients. The longest period of observation was seven months and the shortest three months. Symptoms ranged from mild to severe in various patients. The maintenance dose of Mestinon ranged from 90 to 900 mg. a day. Most patients found that 60 mg. of Mestinon was equivalent to 30 mg. of Neostigmine; they therefore used about half as many tablets of Mestinon.

Twenty-one, or 95%, of the patients preferred Mestinon to Neostigmine. It gave more prolonged effect and evener maintenance of strength than did Neostigmine. Side-effects or toxic reactions were minimal. Mestinon was effective given either alone or in conjunction with ephedrine, potassium, or tetraethylpyrophosphate.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

LYMPHOSARCOMA OF THE SPINAL EPIDURAL SPACE IN A SEVEN-YEAR-OLD CHILD. ERNST A. RODIN, HENRY W. DODGE, and ALVIN B. HAYLES, Proc. Staff Meet., Mayo Clin. **29**:571 (Oct. 27) 1954.

This case is reported because of the youth of the patient, the rapid progression of the illness, the interesting problem in differential diagnosis, the aggravation of symptoms after spinal puncture, and the satisfactory result obtained after prompt institution of appropriate treatment.

A 7-year-old girl first complained of pain in the midportion of her back, radiating around the waist. One week later weakness of the legs developed, so that by the end of the second week she was unable to walk alone. Because of the youth of the patient and the rapid progression of symptoms, and also because of the history of an acute tonsillar infection at the onset of the disease, a neuronitic process of the Guillain-Barré type was considered in the differential diagnostic survey. A diagnostic lumbar puncture was done the morning after the patient's admission. It became evident in the course of the day that a definite rapid increase in the objective neurologic signs had taken place, apparently attributable to the removal of spinal fluid and the changes in pressure relationships within the spinal cord. A iophendylate (Pantopaque) myelogram revealed complete obstruction to the cephalad flow of oil at the 10th thoracic vertebra. Laminectomy was carried out immediately, and an extradural tumor, which proved to be a lymphosarcoma, was found. Extensive subtotal resection of the tumor and wide bony decompression were carried out. The postoperative course was uneventful, and intensive deep roentgen therapy was started 10 days after operation. The child was dismissed one month after admission, showing striking improvement.

At no time during her stay in the hospital was evidence found to suggest the presence of neoplastic tissue in other parts of the body. However, a recent reexamination disclosed that the patient now has clinical and laboratory findings of generalized lymphosarcomatosis.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

SUBARACHNOID TREATMENT WITH NICOTINIC ACID OF SYDENHAM'S ACUTE CHOREA: IMPORTANCE OF IRON METABOLISM. BUSCAINO GIUSEPPE ANDREA, Ann. ital. pediat. **7**:186 (Aug.) 1954.

In 40 cases of Sydenham's chorea, nicotinic acid, administered intrathecally, brought about 30 remissions and very good improvement in eight. The nature of its action is discussed, and the normalization of iron metabolism induced by nicotinic acid is emphasized.

Some peculiar modifications of iron level in blood and cerebrospinal fluid of choreic patients has been described.

Their importance in etiopathogenesis of Sydenham's disease is emphasized.

FROM THE AUTHOR'S SUMMARY.

SOME NEW STUDIES ON THE PROTEINS OF THE CEREBROSPINAL FLUID, USING THE PAPER ELECTROPHORESIS METHOD. F. CORSINI, Clin. pediat. **36**:33 (Jan.) 1954.

Differential analyses were made of the proteins in the cerebrospinal fluids of nine children with acute poliomyelitis. The mean percentages of albumin and of α-, β-, and γ-globulins were within the range found in the cerebrospinal fluids of normal children; but the percentage of γ-globulin varied in the different cases from 4.4% to 17.2%. It would appear that a variation existed in the potential immunity of the different children.

HIGGINS, Boston.

UNUSUAL PSEUDOMYASTHENIA IN A CASE OF POLYMENINGORADICULONEURITIS SPINOMESOENCEPHALICA. O. OLIVI, Clin. pediat. **36**:853 (Nov.) 1954.

An 8-year-old girl developed a neuritis with involvement of the muscles supplied by the cranial nerves; in addition there was a generalized muscular weakness, involving both lower and upper limbs. The case is classified as a pseudomyasthenic spinomesoencephalic variety of the Guillain-Barré-Strohl syndrome.

HIGGINS, Boston.

Psychology and Psychiatry

THE TREATMENT OF TICS IN CHILDHOOD. DAVID M. ZAUSMER, Arch. Dis. Childhood **29**:537 (Dec.) 1954.

This paper forms part of an investigation into the nature, treatment, and prevention of tics in childhood. It is an attempt to appraise the results of treatment of 96 consecutive tiqueurs referred to the Psychiatric Department of the Royal Liverpool Childrens Hospital since May, 1947.

The majority of the parents were anxious, restrictive, and rigid. The conflicting personalities of the parents and tiqueur, and in particular the disturbed mother-child relationship, was found to be a major source of anxiety in the patient. Psychotherapy, in the nature of reassuring the parent as to the mental and physical state of the child is important. In the severer cases treatment was continued weekly at the psychiatric clinic.

KELLY, Milwaukee.

THE PROBLEM MOTHER AND SMALL CHILDREN IN HOSPITALS. BERTIL SÖDERLING, Nord. med. **51**:506 (April 8) 1954.

The author maintains that psychic trauma is common even in children who have been hospitalized for only a short time and have adapted themselves well to hospital life. Prophylactic measures consist of maintenance of contact with the mother in the hospital and at the same time preventing aversion to doctors and hospitals. The author discusses the child's mode of reaction in the hospital. He evaluates the mother's suitability and the routine treatment of sensitive children in hospital and discusses observations on the combination child-mother-hospital-staff.

WALLGREN, Stockholm.

PSYCHIATRIC CONSIDERATIONS ON ADOPTION. SVEN AHNSJÖ, Nord. med. **52**:1499 (Oct. 28) 1954.

A survey is presented of the psychiatric consideration which should be observed in connection with adoption of children. Detailed attention is given to problems of mental hygiene involving the natural parents, the children, and the adoptive parents at different times. Regarding the question of the suitable time of separation of the child from its mother, Ahnsjö takes the limit of 1-2 months required by Bowlby, in relation to the conclusions reached by Spitz and Thysell, and arrives at an acceptable limit at the age of 3-4 months. The psychiatric considerations are regarded of such importance as to make the services of a psychiatrist essential in the diagnosis and treatment of both the natural mother, the adoptive parents, and the child.

WALLGREN, Stockholm.

SOME HOSPITALIZATION PROBLEMS FROM THE POINT OF VIEW OF THE MOTHER. PER SELANDER, Svenska läk.-tidning. **51**:2361 (Sept. 17) 1954.

The author reports a study of psychogenic reactions in children after hospitalization. Eighty-nine per cent of the mothers were satisfied with their children being cared for in separate rooms at the maternity and did not like the rooming-in system. Of 99 mothers who had used the rooming-in system during a previous parturition, 90 were of the opinion that separate rooms for the newborn infants are preferable. Twenty-five per cent of the parents of the children treated at the Flensburg Childrens Hospital believe that the children have been mentally improved during the stay in the hospital. They became quieter and had improved appetite and better sleep. In 11% the parents believed that the children had become mentally worse, especially children belonging to the age group 1-5 years. In 1 child out of 472 it was necessary to consult a physician because of mental troubles that appeared after a hospital stay. In the same group there was about the same incidence of mental illness in sick children treated in their home as in children that had been hospitalized. Of the mothers, 9% believed that it was preferable with no visits, 4% wished to visit their child every day, 2% wanted to visit them once a week. Only 31% were able to visit the hospital every day.

WALLGREN, Stockholm.

Diseases of Genitourinary Tract

FAMILIAL CONSTITUTIONAL PRECOCIOUS PUBERTY IN A BOY THREE YEARS OF AGE: REPORT OF A CASE. EDWARD A. MORTIMER JR., Pediatrics **13**:174 (Feb.) 1954.

A case of familial constitutional precocious puberty in a boy of 3 years is reported, with a brief review of the nine previously described families. In addition, an 11th instance is mentioned.

FROM THE AUTHOR'S SUMMARY.

PRELIMINARY REPORT ON THE PROLONGED INTERMITTENT TREATMENT OF LIPID NEPHROSIS WITH ACTH. E. CHELI and C. MARINI, Clin. pediat. **36**:83 (Feb.) 1954.

Two children, aged 4½ and 5 years, had had nephrosis for 9 months and 2 years, respectively; various methods of treatment had failed to relieve the condition. Then ACTH was given for one week in daily doses of 50 mg., divided into three injections, and then for nine weeks three days a week in the same dosage. The results of this therapy were quite spectacular; there was a marked polyuria, a fall in the proteinuria and in the cholesterolemia, and a rise in the proteinemia and in the albumin: globulin ratio. Electrophoretic serum tracings are reproduced to show the changes in the serum proteins. The therapeutic results have already lasted for four months.

HIGGINS, Boston.

THEORY AND PRACTICE IN THE TREATMENT OF THE NEPHROTIC SYNDROME. P. DURAND and E. DE TONI, Minerva pediat. **6**:48 (Jan. 31) 1954.

The authors give an extensive critical review of the therapeutic results following the various methods of treatment of nephrosis, and especially the antibiotic and chemical procedures wherefrom the deaths from intercurrent infections have diminished. They note that the number of cases cured and of cases which have changed to a more chronic renal insufficiency have been greatly increased.

HIGGINS, Boston.

THE SPEED AT WHICH DYES ARE ELIMINATED BY THE KIDNEYS OF FULL-TERM NEWBORN INFANTS. P. N. SILIQUINI and P. NICOLA, Minerva pediat. **7**:548 (April 28) 1955.

Either indigo carmine or methylene blue was injected into the umbilical veins of a group of 26 newborn infants. The indigo carmine did not appear in the urine until 23 hours later and the methylene blue 27 hours later. It appears that there is a latent period before the kidney of the newborn infant is able to excrete crystalloids of high molecular weight.

HIGGINS, Boston.

THE RESULTS OF A STUDY ON THE SERUM IN INFANTS SUFFERING FROM LIPID NEPHROSIS BY MEANS OF PAPER MICROELECTROPHORESIS. C. HOOFT and R. CLARA, Acta pædiat. **43**:136 (March) 1954.

Serum samples from 9 children with lipid nephrosis, in one case complicated by a renal disease, and from 17 normal children have been analysed by paper microelectrophoresis (procedure of Grassmann and Hannig, apparatus Elphor-H). The distribution of the serum-protein fractions showed in all cases of lipid nephrosis a very low concentration of albumin and an important increase of the α_2-globulin. There is always a decrease of the absolute concentration of γ-globulin. The percentage distribution of the α_1-globulin is somewhat below the normal range. The results obtained for the β-globulin fractions depend on the methods used: they are much higher with an optic apparatus than with the Elphor apparatus. The percentage distribution and the absolute "values" of the different fractions vary considerably from one patient to the other. There is only a slight correlation between the distribution of the different serum protein fractions and the clinical evolution of the edemas. There is no correlation at all between the total protein level and the percentage distribution of the different serum fractions. There is a very apparent correlation between the percentage distribution of the α_2-globulin and the percentages of the albumin. This relationship exists but is less pronounced between the β-globulins and the albumin. It does not exist between the α_1- and γ-globulins and the albumin.

FROM THE AUTHORS' SUMMARY.

Diseases of Ductless Glands; Endocrinology

AN ASSAY METHOD FOR ANTIDIURETIC HORMONE BASED ON A MORE SPECIFIC RESPONSE INDEX. JOHN D. CRAWFORD and BARBARA PINKHAM, Endocrinology **55**:521-529 (Nov.) 1954.

A biologic method for the assay of antidiuretic hormone has been described which differs from the majority of those proposed heretofore in that the index of activity is taken as the change in urine water relative to total osmotically effective solute.

JACOBSEN, Buffalo.

EFFECTS OF ALTERING THE BALANCE BETWEEN PROLACTIN AND OVARIAN HORMONES ON INITIATION OF LACTATION IN RABBITS. JOSEPH MEITES and JAMES T. SGOURIS, Endocrinology **55**:530-534 (Nov.) 1954.

It is concluded that the antagonism between mammary growth and lactation is relative, depending on the balance between the levels of prolactin and the two ovarian hormones in the body. When the mammary growth stimulus exerted by the two ovarian hormones is greater than the lactational stimulus of prolactin, milk flow will be inhibited, and vice versa.

JACOBSEN, Buffalo.

FEMALE PSEUDOHERMAPHRODITISM WITH ADRENOCORTICAL FAILURE IN IDENTICAL TWINS. SULAMMITH WOLFF, Arch. Dis. Childhood **29**:132 (April) 1954.

Female pseudohermaphroditism with adrenocortical failure in identical twins is described.

Cortisone was the main factor preventing death in the neonatal period.

Treatment with salt and DOCA was guided by clinical assessment rather than by biochemical estimations.

When stabilized on salt and DOCA alone, symptoms of adrenocortical failure reappeared in association with intercurrent infections.

Cortisone was started again and continued, primarily with a view to maintaining more adequately the electrolyte balance, so far with gratifying results.

Cortisone should make it possible for the babies to develop as girls.

KELLY, Milwaukee.

ON THE PROGNOSIS OF CRETINISM. DAVID LAWSON, Arch. Dis. Childhood **30**:75 (April) 1955.

It is certain that there is more than one type of nonendemic cretinism, for in a minority of cases the thyroid gland is apparently normal or enlarged. Recent studies suggest that sporadic cretinism without athyrea may be a familial disease. Radiotracer techniques for the study of iodine metabolism offer the hope of further definitions of the two or more diseases which comprise nonendemic cretinism.

KELLY, Milwaukee.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

TRANSIENT SYNOVITIS OF THE HIP JOINT IN CHILDREN. GÖRAN STERNER, Nord. med. **51**:203 (Feb. 4) 1955.

The author describes 19 cases of transient synovitis of the hip joint in chlidren. The youngest child was 10 month of age, the oldest 10 years of age, mean age 4.8 years. The homogenous picture of the disease, the clinical findings, the course of the disease, and the accumulation of cases may point to a contagious etiology. Attempts to demonstrate Coxsackie virus turned out negative. Other infections, trauma, and allergy were found in nine cases. The chief symptoms were pains and limitation of motion, particularly of the intern and extern rotation. The temperature, white blood cell count, and sedimentation rate may be moderately elevated. The antistreptolysin titer was normal; only in a few cases was it elevated. X-ray examination of the hip joint showed no demonstrable lesions of the bone. The treatment is conservative: bedrest and symptomatic measures for relief. The prognosis is excellent.

WALLGREN, Stockholm.

THE DEVELOPMENT OF FUNNEL CHEST. KARL LUDWIG HITZE, Ugeskr. læger **116**:913 (June 17) 1954.

Congenital chondrosternal depression is a part of the anomaly-complex known as mesodysplasia and depends on a faulty myofibrous development of the anterior diaphragm. This produces a disturbance of the normal muscular coordination of the diaphragm, which causes an increased sternal pull and thereby an inspiratory retraction of the chondrosternal portion of the anterior chest wall, which is reversible in infants but fixed in children. This theory of the etiology of funnel chest is in accordance with anthropological, pathological, and experimental experiences.

WALLGREN, Stockholm.

Cutaneous Diseases; Allergy

TYROSINE AS AN ANTI ALLERGIC AGENT. V. W. SPICKARD, Northwest Med. **53**:136 (Feb.) 1954.

A therapeutic agent consisting of *l*-tyrosine, pyridoxine hydrochloride, and Niacinamide was used in the treatment of 135 children showing various proved manifestations of allergy.

The majority showed significant improvement of the allergic conditions.

Further studies as to effect on nutrition are indicated, since the majority of children under continuous treatment for a few months gained in weight at a more rapid rate than formerly.

DOCTOR, Seattle.

SYMMETRICAL DERMATITIS OF PALMS AND SOLES WITH MACROCYTIC ANEMIA. M. K. POLANO and E. VAN ZUIDEN, Maandschr. kindergeneesk. **22**:133 (April) 1954.

The authors describe a symmetric dermatitis of the palms and soles which spread to the arms and trunk, probably caused by a deficiency, in a patient with macrocytic anemia and steatorrhoea.

FROM THE AUTHORS' SUMMARY.

SPONTANEOUS DISAPPEARANCE OF ANGIOMATA. E. V. D. WERF, Nederl. tijdschr. Geneesk. **98**:676 (March) 1954.

Angiomata can be classified on their clinical properties in five categories: (1) nevus araneus, or spider nevus, (2) nevus vasculosus, (3) nevus vinosus, (4) angioma senile, (5) nevus fructosus, or strawberry mark.

The spider nevus tends to regression. Cauterization brings about disappearance without scar formation. The nevus vasculosus tends to fade, but does not disappear. The nevus vinosus has the property of immutability. The number of angiomata senile increases with age. The strawberry mark exists at birth or appears within some days or weeks. It can grow rapidly and become protruding. Then it becomes stationary, and after a period it fades and begins to regress from the center. Most of these marks have disappeared completely at the age of 3-4 years.

Investigations by school health officers showed that florid congenital hemangiomata do not occur among school children. Treatment as a rule is unnecessary. The result of cauterization, excision, or irradiation is often insufficient from a cosmetic point of view. If the mother wants anything to be done, the mark can be covered by an elastoplaster. This causes a constant pressure which seems to be rational.

VAN CREVELD, Amsterdam.

SUN BATHING AND BRASSICA NIGRA. L. FACEE SCHAEFFER, Nederl. tijdschr. Geneesk. **98**:1414-1417 (May) 1954.

After swimming out-of-doors, some children got a fairly serious dermatitis which, however, proved not to be caused by the swimming water, as was thought at first, but by the fruit of Brassica nigra. From this mustard seed mustard oil can be freed after contusion and moistening with water.

VAN CREVELD, Amsterdam.

News and Comment

ANNOUNCEMENTS

International Society of Hematology, Sixth Congress.—The time and location of the Congress will be different from the original announcement. The date has been moved forward one week, to Aug. 26-Sept. 1, inclusive. The convention site has been shifted to the Hotel Somerset, Boston.

The officers of the Congress are as follows: Dr. William Dameshek, President; Dr. James L. Tullis, Vice-President and Treasurer; Dr. William C. Moloney, Secretary; Dr. A. Richardson Jones, Assistant Secretary; Dr. Frank Gardner, Assistant Treasurer.

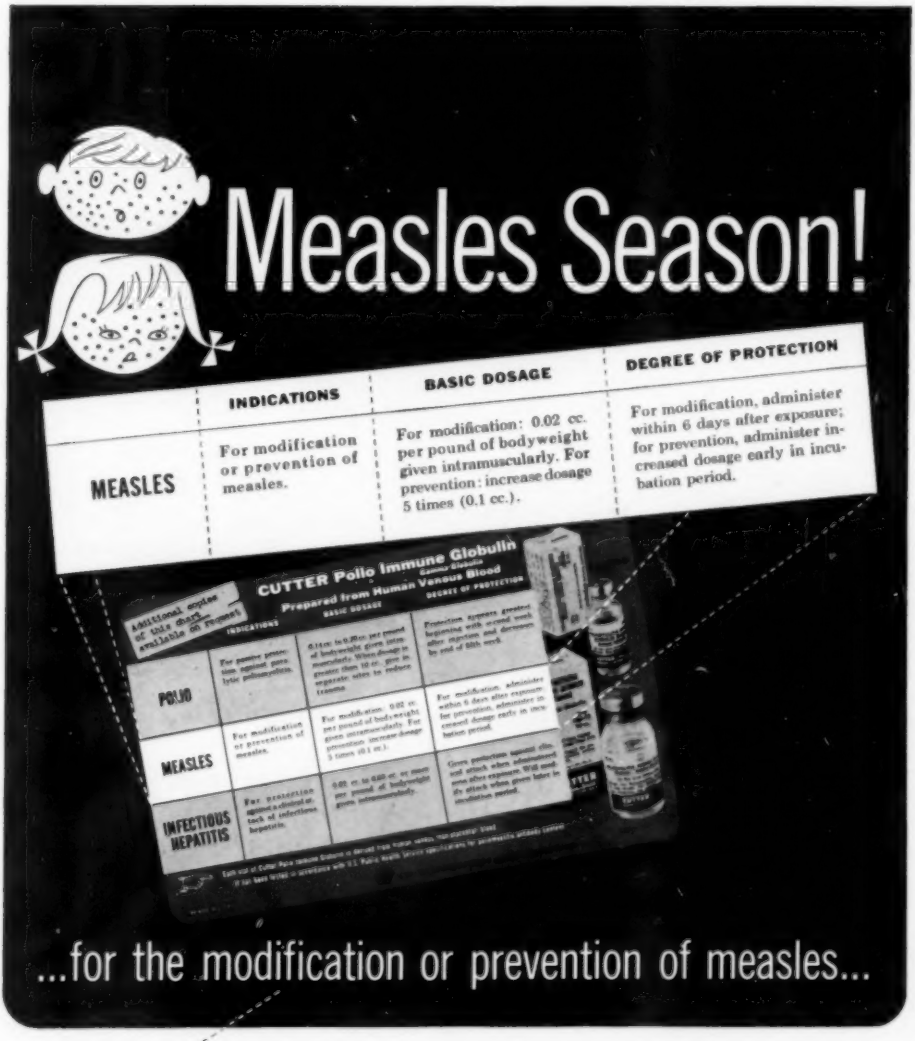
The Sixth Congress of the International Transfusion Society, under the Presidency of Dr. I. S. Ravdin, will be held on Sept. 3-5, inclusive, also at the Hotel Somerset. Combined sessions of the two Congresses are tentatively scheduled for Saturday, Sept. 1, and Monday, Sept. 3. This will permit integration of the immunohematology part of both programs in joint sessions.

The official Travel Agency for the Congress is the World Travel Plan Corp., affiliate of the Hotel Plan of Switzerland. Arrangements for travel may be made directly with World Travel Plan Corp., 125 E. 50th St., New York 22.

Among the speakers who so far have accepted assignments are the following: Leukemia: Joseph H. Burchenal, New York; Giovanni Di Guglielmo, Rome; Alexander Haddow, London; Antoine Lacassagne, Paris; R. Latarjet, France; Samuel Martin, Durham, N. C.; Michael B. Shimkin, Bethesda, Md.; William N. Valentine, Los Angeles. Nucleonics: W. M. Court Brown, London; B. Chr. Christensen, Copenhagen; Clement Finch, Seattle; Leonard Hamilton, New York; W. V. Mayneord, London; Edward H. Reinhard, St. Louis; Joseph F. Ross, Los Angeles; Louis Wasserman, New York. Hemorrhagic Disorders: Tage Astrup, Copenhagen; Kenneth M. Brinkhous, Chapel Hill, N. C.; Erwin Deutsch, Vienna; F. Koller, Zurich; Oscar D. Ratnoff, Cleveland; Walter H. Seegers, Detroit. Anemia: Sheila Callender, Oxford; William B. Castle, Boston; J. B. Marshall Chalmers, Birmingham, England; Sir Stanley Davidson, Edinburgh; Conrad Gasser, Zurich; R. H. Girdwood, Edinburgh; Ludwik Heilmeyer, Freiburg, i. Br.; Hermann Lehmann, London; Carl V. Moore, St. Louis; James Neel, Ann Arbor, Mich.; Wolf W. Zuelzer, Detroit. Immunohematology: J. F. Ackroyd, London; Jean Bernard, Paris; William C. Boyd, Boston; Jean Dausset, Paris; Sabine Filitti-Wurmser, Paris; F. L. J. Jordan, Utrecht; P. Mieschler, Basel; Sven Moeschlin, Solothurn, Switzerland.

Three simultaneous multiple sessions and panel (group) discussions will be held each afternoon (except Wednesday). Ten-minute papers will be followed by discussion. Those desiring to submit papers will please send abstracts (up to 300 words) by March 1, 1956.

Fellowships in Pediatric Cardiology.—One or two fellowships in pediatric cardiology will be available beginning July, 1956, at The Children's Orthopedic Hospital, Seattle. Training will be in conjunction with the Department of Pediatric Cardiology, University of Washington School of Medicine. Salary open. Desire applicants with minimum of two years of pediatrics. Direct correspondence to Robert A. Tidwell, M.D., The Children's Orthopedic Hospital, 4800 Sand Point Way, Seattle 5.


Measles Season!
INDICATIONS
BASIC DOSAGE
DEGREE OF PROTECTION
MEASLES
For modification or prevention of measles.
For modification: 0.02 cc. per pound of bodyweight given intramuscularly. For prevention: increase dosage 5 times (0.1 cc.).
For modification, administer within 6 days after exposure; for prevention, administer increased dosage early in incubation period.
CUTTER Polio Immune Globulin
Prepared from Human Venous Blood
POLIO
MEASLES
INFECTIOUS HEPATITIS
...for the modification or prevention of measles...

Cutter Polio Immune Globulin

- Derived from human venous blood—crystal clear.
- Produced by Cutter Laboratories, first to offer gamma globulin commercially.
- Tested in accordance with U. S. Public Health Service specifications for poliomyelitis antibody content.
- For measles, polio, infectious hepatitis, and agammaglobulinemia.

For copies of the dosage chart illustrated above, write:

CUTTER Laboratories
BERKELEY, CALIFORNIA

FIRST to produce blood fractions commercially

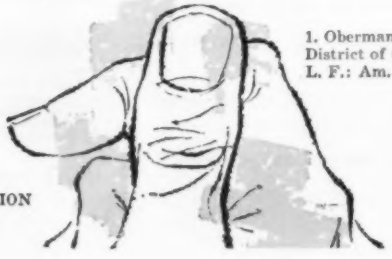
either way you win with Bremil®

"heads"... because a BREMIL formula provides a *complete* nutritional intake that consistently promotes infant growth and development at or above accepted standards[1]; made with grade A milk.

"tails"... because the easily digested, efficiently utilized protein content of BREMIL (approximating that of breast milk) virtually eliminates excoriations due to ammonia dermatitis[1], and does not impose an excessive solute load on the immature kidney[2]

Standard Dilution

One level measure to 2 fluidounces of hot water. Mixes like a liquid. Costs no more than ordinary formulas requiring vitamin and carbohydrate supplementation. In 1-lb. tins at all drug outlets.



1. Oberman, J. W., and Burke, F. G.: M. Ann. District of Columbia 23:483, 1954. 2. Hill, L. F.: Am. J. Clin. Nutrition 3:75, 1955.

Borden's®

PRESCRIPTION PRODUCTS DIVISION
350 Madison Avenue, New York 17

New urethral suppositories relieve pain and combat infection

***The child's activities continue—treatment is "...shorter and more comfortable than the conventional method..."*[1]**

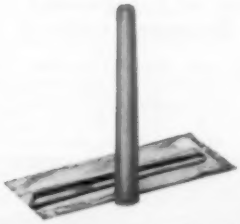
- relieve pain and burning promptly
- kill most bacteria common to urethral infections
- easy for mother to insert at home
- irritation rare in over 340 cases (adults)[1]

PRESCRIBE: for bacterial (granular) urethritis, for topical anesthesia and prophylaxis of infection before and after instrumentation

FURACIN vaginal suppositories

To prevent urethrovaginal cross-infection, "Furacin suppositories are inserted in the urethra daily, if practical, and inserted in the vagina each night for a week."[2] Formula: Furacin, 0.2% in a water-miscible base.

References: 1. Youngblood, V. H.: J. Urol. 70:926, 1953. 2. Carroll, G.: Pediat. Clin. N. America, 1956, pp. 781-791.



FURACIN®
BRAND OF NITROFURAZONE
urethral
SUPPOSITORIES

Formula. 0.2% Furacin (brand of nitrofurazone), 2% diperodon•HCl in water-miscible base. Sealed in foil. Box of 12.

EATON LABORATORIES, Norwich, N.Y. **NITROFURANS** a new class of antimicrobials neither antibiotics nor sulfas

New Book Suggestions for the Pediatrician's Library

●

Pediatric X-ray Diagnosis—Caffey

New 3rd Edition—A sweeping revision, including 382 new illustrations, has brought this classic work up to the minute. There are new or rewritten sections on congenital dysplasia and dislocation of the hip, congenital heart disease, megacolon, Perthes' coxa plana and slipping of upper femoral epiphysis, etc. The new edition features 2264 illustrations on 1267 figures, also new tables for estimation of maturation of the skeleton.

By John Caffey, M.D., College of Physicians and Surgeons, Columbia University. 1059 pages; 2264 illustrations on 1267 figures. $28.00

Advances in Pediatrics—Levine

New Vol. 8—Seven monographs of top interest to all physicians dealing with children are presented in the just-published Volume 8 of Advances in Pediatrics. By title they are: Etiology of Infantile Diarrhea; Isosexual Precocity in Boys, Including a Case of a Gonadotropin-Producing Teratoma; Sarcoidosis in Childhood; Offspring of Diabetic and Prediabetic Mothers; Subdural Lesions in Childhood, with Special Reference to Infectious Processes; Prevention of Accidents in Childhood; Mental Deficiency.

Edited by S. Z. Levine, M.D., Cornell University Medical College. Associate Editors: John A. Anderson; Margaret Dann; A. Ashley Weech; Myron E. Wegman; Warren E. Wheeler; 273 pages; 47 illustrations; 19 tables. $8.00

Diagnosis of Congenital Heart Disease—Kjellberg, et al

New—Here are the techniques (including the high-speed angiocardiographic method), evaluations and interpretations of the Cardiac Team at the famous Pediatric Clinic of Karolinska Sjukhuset, Stockholm—presented in a magnificently illustrated volume which shall surely become a classic. A full description is given of clinical features and physical signs and their integration with technical methods of examination.

By Sven Roland Kjellberg, M.D., Edgar Mannheimer, M.D., Ulf Rudhe, M.D., and Bengt Jonsson, M.D., Karolinska Sjukhuset, Stockholm. 641 pages; 1845 illustrations on 618 figures. $22.00

The Year Book Publishers
200 E. Illinois St., Chicago 11, Ill.

Year Book PUBLISHERS

Please send for 10 days' examination.

- ☐ Caffey's Pediatric X-ray Diagnosis, $28.00
- ☐ New Volume 8, Advances in Pediatrics, $8.00
- ☐ Diagnosis of Congenital Heart Disease, $22.00

Name ..... Street .....

City ..... Zone..... State.....

AJDC 3-56

YOUR GUIDE TO CURRENT PUBLICATIONS

Quarterly Cumulative Index Medicus

WITH AUTHORS AND SUBJECTS...

Divided into sections, one devoted to books and the other to periodical literature, the QUARTERLY CUMULATIVE INDEX MEDICUS contains a list of current publications alphabetized as to authors and subjects. The exact bibliographic reference is given under the author with titles in the original language, while titles under subjects are all in English. The index also includes a listing of journals, their addresses and publishers.

The QUARTERLY CUMULATIVE INDEX MEDICUS appears twice a year; volumes are cloth bound and cover periodicals for six months as indicated on the publication. These two volumes are a convenient and reliable reference for current medical literature. Invaluable for practitioners, specialists, teachers, editors, writers, investigators, students and libraries.

SUBSCRIPTION PRICE
$25.00 PER YEAR
CANADIAN AND FOREIGN
$27.00 PER YEAR

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS

Why Selby shoes for children cost just a little more

The only genuine Arch Preserver Shoes for children

Selby Junior Arch Preservers cost slightly more than other children's shoes because they are made of only the very finest leathers, and because it requires more care to make them.

Doctors know that parents expect to pay just a little more for the best shoes their children can wear. And doctors prescribe Selby Junior Arch Preservers because they want their patients to wear the best shoes made for children in America today.

The excellence of Selby Junior Arch Preservers is the result of the knowledge and skill acquired in more than three quarters of a century of fine shoemaking.

When you recommend shoes for infants and children, please remember—Selby Juniors are the only *genuine* Arch Preserver Shoes for children. Recommend them with confidence.

• *If Selby Junior Arch Preservers are not available in your city, please write directly to us.*

The Selby Shoe Company
Portsmouth, Ohio

Selby
JUNIOR ARCH PRESERVER
Shoes

MORE THAN THREE QUARTERS OF A CENTURY OF FINE SHOEMAKING

*Specially processed non-diastatic malt extract neutralized with potassium carbonate. In 8 oz. and 16 oz. bottles.

Send for Samples and Literature

For HARD, DRY STOOLS OF CONSTIPATED BABIES

Borcherdt

MALT SOUP Extract*

A gentle laxative modifier of milk. One or two tablespoonfuls in the day's formula—or in water for breast fed babies—produce a marked change in the stool.

SAVES DOCTOR'S TIME, TOO!

Fewer phone calls from anxious mothers. Malt Soup Extract is merely added to the formula. Prompt results. Easy for mother to prepare and administer. Does not upset the baby.

BORCHERDT MALT EXTRACT CO.

217 N. Wolcott Ave. • Chicago 12, Ill.

AN APPROVED EDUCATION

FOR HOME - BOUND CHILDREN

Famous Calvert School-at-Home Courses for Kindergarten through 9th Grade

Physicians recognize the therapeutic value of the school routine for youthful patients. Many handicapped children show marked progress toward normal health when home-study courses are introduced. Thousands now get their elementary school education in their own homes with the famous Calvert *School-at-Home* Courses. Children afflicted by crippling orthopedic conditions, cerebral palsy, rheumatic fever, impaired hearing use the Calvert Courses on their doctor's recommendation. Calvert materials are complete in every detail—teaching manual, lessons, books and supplies. They are easily adapted to the child's mental, physical, emotional capabilities.

Calvert Courses are available for Kindergarten through 9th grade. They stimulate interest and curiosity. They permit children to advance at their own pace. More than 100,000 children have been taught by the Calvert method in the past 50 years. Calvert Courses are approved by the Maryland Department of Education.

Help parents of handicapped children solve difficult educational problems. Recommend Calvert *School-at-Home* Courses with confidence. Complete information sent promptly on request.

CALVERT SCHOOL

570 Tuscany Road Baltimore 10, Md.

BOOKLETS ON MENTAL HYGIENE

Here are several booklets on mental hygiene that may prove of interest and use to you and your patients.

EMOTIONAL HEALTH IN WORK AND PLAY. T. R. Retlaw. 8 pages. 15 cents.

MESMERISM MINUS MESMER. Stefan Zweig. A discussion of hypnotism. 5 pages. 5 cents.

JOE'S NERVOUS BREAKDOWN. John E. Eichenlaub. 6 pages. 10 cents.

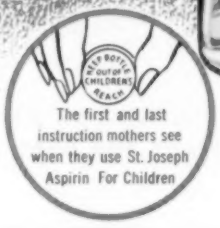
YOUR STAKE IN MENTAL HEALTH. George S. Stevenson. 4 pages. 10 cents.

WHERE MENTAL PATIENTS RULE THEMSELVES. Murray Teigh Bloom. 4 pages. 10 cents.

Keep a supply of these booklets on hand. Available at lower cost for quantity purchases.

AMERICAN MEDICAL ASSOCIATION
535 North Dearborn Street
Chicago 10, Illinois

"...first aspirin taken readily by my own children"



The first and last instruction mothers see when they use St. Joseph Aspirin For Children

When a doctor writes that St. Joseph Aspirin For Children is the "... first aspirin taken readily by my own children," we feel there could hardly be a higher tribute to the exceptional palatability of these specialized aspirin tablets.

For purity, palatability, potency and therapeutic effectiveness, St. Joseph Aspirin For Children is unsurpassed for salicylic administration in infancy and childhood.

Physicians are finding St. Joseph Aspirin For Children:

1. *Easy to give*
2. *Pleasant to take*
3. *Therapeutically Effective*

ST. JOSEPH ASPIRIN FOR CHILDREN

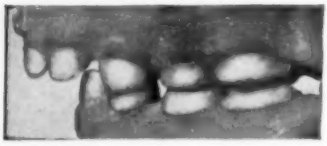
A Palatable Aspirin Tablet of Unique Excellence

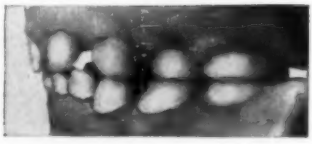
Plough, Inc.

If you have not received samples, write to Plough, Inc., Memphis, Tennessee

THUMBSUCKING

since infancy caused this 4 year old's malocclusion.





THUM
TRADE MARK

THUM broke the habit and teeth returned to normal position in 9 months.

THUM DISCOURAGES NAIL BITING TOO

GET THUM AT YOUR DRUGGIST OR SURGICAL DEALER.
PRESCRIBED BY PHYSICIANS FOR OVER 20 YEARS.

THE PEDIATRIC DEPARTMENT
of
MEMORIAL CENTER FOR CANCER AND ALLIED DISEASES

announces that

The annual comprehensive three day course in Pediatric Oncology
for
PEDIATRICIANS, GENERAL PRACTITIONERS, HEALTH OFFICERS
will be held
April 25, 26 and 27, 1956

PURPOSE: To review current concepts regarding the neoplastic diseases of children particularly as to diagnosis, differential diagnosis and management, and to indicate the importance of the clinician's role in the control of cancer in childhood.

METHOD: Case demonstrations, clinics, lectures given by the following Services: Gastric and Mixed Tumor, Bone, Thoracic, Radiology, Pediatrics, Chemotherapy, Gynecology, Radiology, Head and Neck, Genito-Urinary, and Neurosurgical.

FACULTY: Twenty members of the Attending Staffs of Memorial Hospital and Sloan-Kettering Institute for Cancer Research.

TIME: 8:30 a.m. to 4 p.m.

PLACE: Children's Pavilion, Memorial Center

FEE: $35.00 Class limited to 15 physicians.

For information address:

DIRECTOR, PEDIATRIC SERVICE
MEMORIAL CENTER
444 EAST 68th STREET NEW YORK, NEW YORK

. . . interesting information for your patients

. . . reinforcements for your own verbal instructions

The A. M. A.'s Bureau of Health Education offers pamphlets on most any subject . . . such as these three articles on old age:

HOPE FOR THE AGED
James A. Brussel
4 pp. 10¢

THE PROMISE OF GERIATRICS
T. C. Desmond
16 pp. 20¢

STILL LOOKING AHEAD
28 pp. 15¢

You may obtain a catalogue by writing to:

A.M.A. BUREAU OF HEALTH EDUCATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS

3 steps

to a well-balanced formula

in accordance with the needs of the infant

VARAMEL*

+

CARBOHYDRATE

+

WATER

*Made from Grade A Milk (U. S. Public Health Service Milk Code) which has been modified by replacement of the milk fat with animal and vegetable fats and by the addition of synthetic vitamins. No carbohydrate has been added.

Approximate Analysis

Protein	4.9%
Carbohydrate	8.3
Fat	5.8
Ash	1.2
Calcium	0.19
Phosphorus	0.15
Iron	0.0016
Moisture	79.8
Calories per fl. oz.	32

THE BAKER LABORATORIES, INC.

Milk Products Exclusively for the Medical Profession

MAIN OFFICE: CLEVELAND 3, OHIO • PLANT: EAST TROY, WISCONSIN

to help you combat iron deficiency in infants...

How Fer-In-Sol improved infants' blood pictures

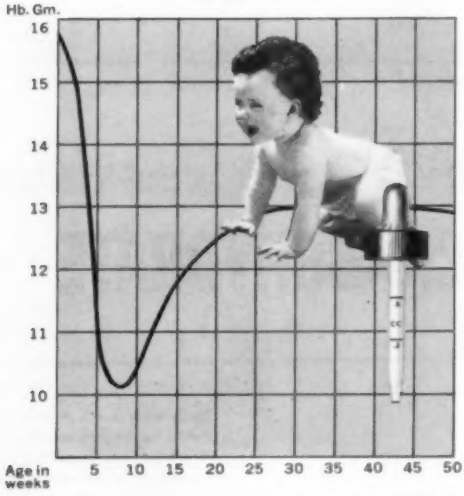


Chart adapted from Niccum, Jackson and Stearns: A.M.A. Am. J. Dis. Child. 86: 553, 1953.

Mean hemoglobin determinations of infants on a predominantly milk diet receiving Fer-In-Sol. The Fer-In-Sol dose was 5 mg. of iron (0.2 cc.) per day at 3 months, increased to 10 mg. of iron (0.4 cc.) after 6 months of age.[1]

Fer-In-Sol

iron in a drop for infants and children

"Iron deficiency anemia has a peak incidence between six months and two and one-half years..."[2]

Smith and Rosello[3] found that the peak incidence of iron deficiency in infants and children occurred between the ages of 6 and 24 months, when growth is most rapid. Sturgeon[4] reports that published data indicate iron deficiency in infants is common. Although consuming normal diets, the majority of infants in the last half of the first year of life, and throughout the second year of life, "exist in relatively severe states of iron deficiency (30% or more depleted)."[4]

Niccum, Jackson and Stearns[1] found that prophylactic administration of Fer-In-Sol in small daily doses "was sufficient to maintain hemoglobin values at a constant level throughout the latter half of infancy in all full term infants"... resulted in significantly higher hemoglobin values than did ferric ammonium citrate.

FER-IN-SOL

Fer-In-Sol® provides a pleasant way to supply ferrous sulfate—a well tolerated, well absorbed and efficiently utilized form of iron. The vehicle is acidulous to improve absorption and utilization. The good taste of the solution makes it readily acceptable to young children. And tolerance is good.

Only 0.3 cc. of Fer-In-Sol supplies 7.5 mg. of iron—more than the Recommended Daily Allowance for children up to 4 years old. Fer-In-Sol is supplied in 15 cc. and economical 50 cc. bottles, with the new calibrated 'Safti-Dropper' of unbreakable plastic.

(1) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 86: 553, 1953. (2) Smith, C. H.: Bull. New York Acad. Med. 30: 185, 1954. (3) Smith, N. J., and Rosello, S.: J. Clin. Nutrition 1: 275, 1953. (4) Sturgeon, P.: Pediatrics 13: 107, 1954.

MEAD

SYMBOL OF SERVICE IN MEDICINE

MEAD JOHNSON & COMPANY, EVANSVILLE 21, INDIANA, U.S.A.

Throughout the world...

use in millions of cases and reports by thousands of physicians have built confidence in TERRAMYCIN®

BRAND OF OXYTETRACYCLINE

. . . a well-tolerated, rapidly effective broad-spectrum antibiotic of choice.

Capsules, tablets, taste-tempting liquid forms and special preparations for parenteral, topical and ophthalmic use.

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

For Nasal
Congestion in Children
Neo-Synephrine, a gentle, dependable decongestant for colds, sinusitis, hay fever and allergic rhinitis, is now available in a form especially well suited for children:
NEO-SYNEPHRINE®
Hydrochloride 0.25%
Pediatric Nasal Spray
Unbreakable plastic • Uniformly fine mist
Leakproof
Small pocket size • No sting • No fuss
Contains Zephiran® Cl 0.02% (1:5000), antibacterial wetting agent and preservative for greater efficiency.
Children easily learn to use Neo-Synephrine Pediatric Nasal Spray themselves with adult supervision. Also suitable for adults who prefer a mild nasal spray.
Squeeze bottles, 20cc.
Winthrop LABORATORIES
NEW YORK 18, N.Y. • WINDSOR, ONT.